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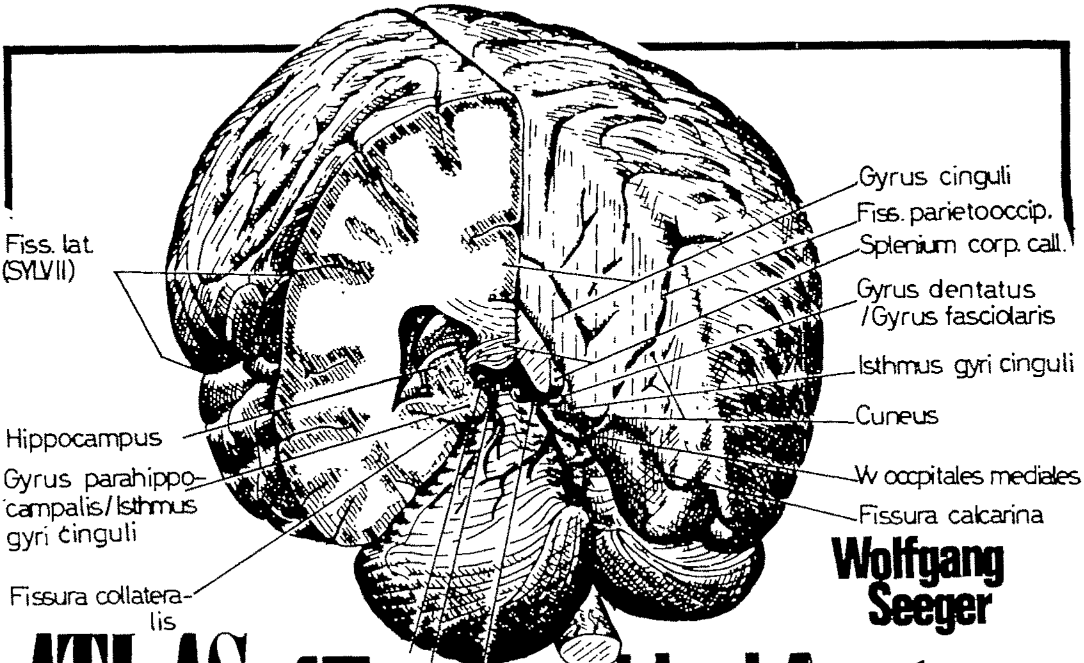

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NEUROPHYSIOLOGICAL ASPECTS OF PATTERN-SENSITIVE EPILEPSY

by A. J. WILKINS, C. E. DARBY *and* C. D. BINNIE

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INTRODUCTION

ABOUT 5 per cent of patients with epilepsy are photosensitive; that is, paroxysmal activity can be elicited in the EEG by conventional intermittent photic stimulation (IPS) using a stroboscope (Jeavons and Harding, 1975, p. 3). In more than half these patients paroxysmal activity can also be induced by the viewing of striped patterns (Stefansson, Darby, Wilkins, Binnie, Marlton, Smith and Stockley, 1977). The present investigation describes the characteristics of a pattern that render it epileptogenic and, on the basis of recent work on the physiology of pattern vision, adduces evidence for the hypothesis that visually-induced paroxysmal EEG activity can be triggered in the striate cortex by the synchronized firing of large numbers of cells, the probability of paroxysmal activity being related to the number of cells stimulated. The hypothesis is an extension of that proposed by Wilkins, Andermann and Ives (1975) on the basis of a single case study.

Three of the studies in this paper report replications of the findings of Wilkins, Andermann and Ives (1975). The remainder provide confirmatory evidence for the hypothesis, and allow the interpretation of their findings to be elaborated.

METHODS

General Methods

Procedure. In all studies the procedure was broadly similar. The procedure for individual experiments will therefore be reported only in so far as it differed from the description that follows.

The patient was seated in a chair while the EEG was recorded, and was instructed to look at a variety of visual stimuli, wearing spectacles if they had previously been prescribed. The stimuli were successively presented in random order, the order constrained so that all stimuli were presented n times before any stimulus received its $(n+2)$th presentation. A stimulus was removed as soon as any paroxysmal activity appeared or when a presentation period had elapsed without any such activity. The period was usually 10 s and there was an interval of at least 5 s between presentations. Every four minutes or so, the patient was given a longer break in which to rest. Provided the patient was willing, the presentations continued in this manner until a significant variation in the incidence of paroxysmal activity in response to the various stimuli had emerged.

Most of the patients studied were unaware of the occurrence of paroxysmal activity, and only rarely was the activity accompanied by any clinical signs. A major seizure was induced on one occasion only, as a result of conventional IPS.

Patients. The patients who participated in the nine studies are listed in Table 1 which presents the age, sex, type of epilepsy and type of resting EEG activity for each patient. The majority of patients were attending the Instituut voor Epilepsiebestrijding, Heemstede, Netherlands, 7 as outpatients and 3 as inpatients. Five patients were outpatients seen at the EEG Department, Runwell Hospital, Essex, UK and the remaining patient was attending the Montreal Neurological Institute, Canada. The patients were selected on the basis (1) that they were willing to take part in the study, and (2) that photic stimulation and patterns had induced paroxysmal activity during previous routine diagnostic EEG examinations. All of the patients were receiving anticonvulsant medication at the time of examination.

Screening tests. Photic stimulation techniques were standard in so far as every patient received stimulation in a darkened room at frequencies between 6 and 40 Hz (including stimulation in the range 16 to 18 Hz) using an unpatterned photic stimulator which provided a mean luminance of at least 1500 cd/m^2, and which was centrally fixated at a distance of 30 cm from the nasion, subtending at least 28 degrees. Pattern stimulation always included stimulation with square-wave gratings, mean luminance 300 cd/m^2, contrast 0·75, circular in outline and subtending at least 24 degrees, with spatial frequencies including 2 cycles/degree.

EEG analysis. The EEG response to visual stimulation was regarded as positive when bursts of spikes or slow waves or both appeared, with the exception of occipital spikes which were disregarded (Jeavons and Harding, 1975, p. 58). In every patient a response that could broadly be described as spike-wave or multiple spike-wave was elicited by visual stimulation of one kind or another. However, the morphology and topography of the response appeared to depend on the nature of the visual stimulus. It is beyond the scope of this paper to describe in detail the relationship between the visual stimulus and the type of EEG response. Suffice it to say that stimuli that readily elicited paroxysmal activity tended to induce generalized activity, whereas less provocative stimuli would often elicit activity confined to the posterior regions. In no patient was the activity confined to the anterior regions.

Study 1. Effects of Spatial Frequency

At threshold the contrast sensitivity of the human visual system to square-wave gratings is maximal at frequencies of around 4 cycles/degree (Campbell and Robson, 1968). The amplitude of the late positive wave of the evoked potential in response to sine-wave gratings is also maximal at these frequencies (Parker and Salzen, 1977). The question of immediate interest is therefore whether the patterns that are optimal stimuli for inducing paroxysmal EEG activity in photosensitive patients have a similar spatial frequency.

Procedure. Prints of square-wave gratings, circular in outline, 24 cm in diameter, with 0·5, 1, 2, 4 and 8 cycles/cm were dry-mounted on cards. The patient was seated 57 cm from a screen illuminated by a projector and the cards held rigidly against this screen. One centimetre of the pattern thus subtended one degree of visual angle. The gratings had a mean luminance of 300 cd/m^2 and a contrast of 0·75. The following patients took part in the study: M.V.D.H., V.L.N., V.L.P., M.W., D.E., H.V.L.D., H.S. and V.D.U.

TABLE 1. SUMMARY OF PATIENTS' DETAILS

Patient	*Age (yrs)*	*Sex*	*Classification of epilepsy*[1]	*Factors known to precipitate seizures*	*Resting EEG*	*Snellen acuity*
D.E.	9	F	Primary generalized	TV	Generalized and postcentral multiple spike-wave	Not tested
G.F.	16	M	Primary generalized	TV	Brief generalized multiple spike-wave	R 6/6 L 6/6
H.S.[2]	26	M	Secondary generalized	Patterns	Theta dominant	Not testable
H.V.D.[2, 3]	42	M	Secondary generalized	TV	Excess theta activity	R 6/12 L 6/12
H.V.L.D.[2]	28	M	Secondary generalized	TV, patterns, flicker, fluorescent lighting (self-induction)	Slow generalized spike-wave	R 6/18 L 6/18
K.O.	10	F	Primary generalized	TV	Generalized multiple spike-wave	Not tested
K.W.[4]	16	M	Primary generalized	TV	Rare generalized multiple spike-wave	R 6/6 L 6/6
L.D.	12	F	Primary generalized	TV, patterns	Generalized spike-wave	Not tested
M.T.	15	F	*See* Wilkins, Andermann and Ives (1975)			
M.V.D.H.	12	F	Primary generalized	TV	Normal	R 6/7·5 L 6/7·5
M.W.[4]	10	M	Primary generalized	TV	Normal	R 6/7·5 L 6/7·5
S.N.	9	F	Primary generalized	TV	Generalized and postcentral multiple spike-wave	Not tested
S.P.	22	F	Primary generalized	Patterns, fluorescent lighting, cinema	Normal	R 6/6 L 6/6
V.D.U.	18	F	Partial	TV, flicker, patterns	Normal	R 6/6 L 6/6
V.L.N.	10	F	Primary generalized	—	Posterior spike-wave in drowsiness	Not tested
V.L.P.	16	F	Primary generalized	TV	Generalized spike-wave	R 6/5 L 6/5

[1] Merlis (1970). [2] Subnormal. [3] Hemiparetic. [4] Brothers.

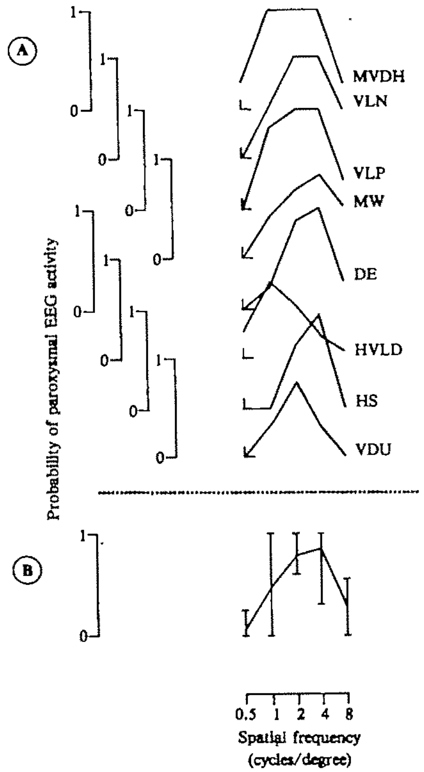

FIG. 1. Probability of paroxysmal EEG activity as a function of the spatial frequency of a square-wave grating, subtense 24 degrees, contrast 0·75, mean luminance 300 cd/m². A, individual patients, B, group data. Bars indicate range.

Results. The incidence of paroxysmal activity for the 8 patients is summarized in fig. 1A. The number of observations per point averaged 9·4 with a minimum of 4. Fig. 1B shows the mean estimates for the patient group with the ranges of values obtained. When the sensitivity to the five spatial frequencies was ranked separately for each individual patient the concordance between patients was highly significant ($W = 0{\cdot}74$, $P < 0{\cdot}01$), the optimum spatial frequency lying between 1 and 4 cycles/degree in all cases.

Discussion. The spatial frequency optimum for inducing paroxysmal activity lay between 1 and 4 cycles/degree for every patient tested. This result for high contrast stimuli mirrors the well-known peak sensitivity of the visual system to gratings at threshold contrast. It also accords well with the subtense at which the maximum amplitude of the late positive wave of the evoked potential is obtained with a 6 degree field using sine-wave gratings (Parker and Salzen, 1977). The functions relating probability of paroxysmal activity to spatial frequency are steep. The slope at the low frequency end is more marked than might be anticipated from a straightforward model based on the component spatial frequencies of a square-wave grating (Soso and Lettich, 1978). This point will not be discussed in detail here because, given present knowledge, it can tell us little about the locus and nature of the seizure trigger.

Study 2. Effects of Grating Orientation

One of the four cases of pattern sensitivity described by Chatrian, Lettich, Miller and Green (1970) demonstrated a marked orientation selectivity favouring vertical gratings. The second study was therefore designed principally as a preliminary experiment to determine whether for a population of pattern-sensitive patients the vertical orientation was more likely to be epileptogenic. The concern was not to investigate in detail any orientation selectivity that individual patients might show.

Procedure. Square-wave gratings with a spatial frequency of either 2 or 4 cycles/degree were shown in four orientations: horizontal, vertical and the two 45 degree obliques, using procedure and stimuli similar to those of the first study. Patients M.V.D.H., V.L.N., V.L.P., M.W., D.E., H.V.L.D., H.S. and V.D.U. took part.

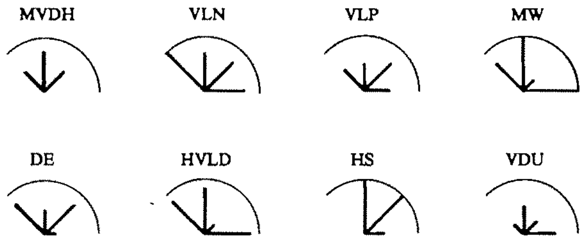

FIG. 2. Probability of paroxysmal EEG activity as a function of the orientation of a square-wave grating, subtense 24 degrees, contrast 0·75, mean luminance 300 cd/m^2, spatial frequency 2 cycles/degree (V.D.U, 4 cycles/degree). The length of the lines is proportional to the probability and the radius of the arc represents a probability of 1·0.

Results. The incidence of paroxysmal EEG activity for the four pattern orientations is shown separately for each patient in fig. 2. It will be seen that for the group as a whole there is no tendency for one orientation to be more epileptogenic than the others (Kendall's W = 0·036, $P \gg 0{\cdot}05$).

Two patients, H.S. and M.V.D.H. demonstrated a significant difference in sensitivity to the four orientations. Neither of these patients had been prescribed spectacles. In the case of H.S., retinoscopy revealed a marked astigmatism 3·5 D at 170° in the right eye, 1·0 D at 0° in the left. Subjective testing of M.V.D.H. using gratings with a high spatial frequency suggested an astigmatism favouring a vertical over a horizontal axis. Since the probability of paroxysmal activity is reduced when patterns are poorly focused (Chatrian *et al.*, 1970) the astigmatism may be sufficient to account for the orientation specificity, given that in both cases the orientation of the axis was appropriate.

Discussion. For the group as a whole no one orientation was more epileptogenic than the others. Individual patients did, however, demonstrate significant orientation selectivity, possibly as a result of an astigmatism. Cases with orientation selectivity existing independently of astigmatism have yet to be demonstrated and would require more intensive investigation than has so far been attempted. However, the present study is sufficient to emphasize that clinical investigations for pattern sensitivity should include testing with patterns in a variety of different orientations.

The studies described so far have looked at some of the obvious parameters of patterns. These parameters tell us relatively little about mechanisms. The studies that follow take advantage of the information acquired and seek to delimit the number of possible alternative physiological mechanisms, replicating and extending the work of Wilkins *et al.* (1975).

Models of the Photoconvulsive Response

The visual system is conventionally thought of as consisting of a major pathway from the eye to the visual cortex via the lateral geniculate nucleus of the thalamus (LGN), and pathways to the superior colliculus directly from the eye and indirectly via the visual cortex. The major pathway is comprised of X (so-called sustained) and Y (so-called transient) systems. The direct and indirect pathways to the superior colliculus involve only Y neurons. For paroxysmal EEG activity to be evoked by visual stimulation, abnormal neural activity must be precipitated by the action of cells within the LGN, cortex and/or superior colliculus. This is not to say that any component of the visual system itself necessarily functions abnormally.

Bickford, Daly and Keith (1953) in their discussion of the hypothetical pathways for the convulsive response to light proposed three alternatives: (1) a transcortical pathway originating in the visual cortex; (2) a corticothalamic pathway from visual cortex to a thalamic system with diffuse projections to cortex; and (3) a subcortical thalamic pathway from the LGN to the diffuse thalamic system. Bickford *et al.* did not include a pathway from the superior colliculus, although there is no obvious reason for its omission. The first and second of the above alternatives involve the visual cortex, accessed via the normal pathways, and responsible via abnormal pathways for initiating directly in the first case and indirectly in the second, a generalized cortical disturbance. The difficulty with these models is that it is not specified how the abnormal pathways are responsible for the abnormal neural activity.

A simple alternative hypothesis to those proposed by Bickford *et al.* would be that the cortex is for some reason generally hyperexcitable, possibly as the result of the malfunction of a system involving an inhibitory neurotransmitter such as GABA (Meldrum and Balzamo, 1972). Any means of causing large numbers of neurons to fire synchronously may, in such a brain, be sufficient to induce spike trains (Calvin, 1975). However, in *Papio papio*, the photosensitive baboon, intermittent light stimulation triggers bilateral spike and wave discharges specifically in frontal or frontocentral regions. These discharges may spread initially in the anterior cortical areas and the underlying subcortical region, subsequently to the internal capsule, pons and brain-stem and the discharges may ultimately invade all the deep structures except the rhinencephalon. Thus a definite progression of the discharge is seen and the pathways for the spread of the discharge do not involve the visual cortex. Nevertheless the visual cortex appears to be an important link in the pathway from retina in as much as its removal results in the loss of photosensitivity (*see* Naquet, Catier and Menini, 1975, for review).

In the light of the above it is difficult to synthesize a coherent theoretical viewpoint, although as a preliminary hypothesis it might be fair to suppose that pathways from the occipital cortex are responsible for the generation of generalized activity in hyperexcitable cortex. Such a hypothesis would be quite consistent with the known characteristics of the occipital spike, a precursor of paroxysmal activity that often occurs in the EEG of photosensitive patients (Jeavons and Harding, 1975, p. 94).

The remainder of this paper uses the characteristics that render visual stimuli epileptogenic to make inferences about where and how in the visual system the seizures are triggered. The inferences are based in part on the assumption that the characteristics of the receptive fields of cells in the visual system of the photosensitive patient resemble those of cells recorded in monkey or in some instances in cat. This assumption is warranted in so far as there is no evidence to suggest that the visual system of photosensitive patients is itself abnormal: pattern sensitive patients can have quite normal acuity for gratings at threshold contrast (Soso and Lettich, 1978).

Study 3. Effects of Colour Contrast at Isoluminance

Wilkins *et al.* (1975) found that square-wave gratings composed of alternate red and green stripes failed to elicit paroxysmal activity, whereas a pattern of similar dimensions with black and white stripes (luminance contrast 0·8) readily did so. In 7 patients subsequently tested a similar result has been obtained.

Procedure. A vertical square-wave grating, circular in outline and 24 cm in diameter, with 3 cycles/cm, was produced by juxtaposing alternate strips of red and green matt opaque tape (1/16″ Letratape). The pattern was held against a support in the beam of a projector and had a mean luminance of 200 cd/m^2. Seven patients, K.W., M.V.D.H., M.W., V.L.P., V.D.U., D.E. and H.V.L.D., who were known to be sensitive to gratings with spatial frequencies of 2 and 4 cycles/degree were presented with the coloured pattern at a viewing distance of 57 cm, at which distance it had a spatial frequency of 3 cycles/degree.

Results. No paroxysmal activity was elicited by the coloured pattern, despite an average of 7 presentations per patient (minimum 4), and despite the fact that 4 of the patients were sensitive to black and white gratings with mean luminance 130 cd/m^2 and contrast 0·4. Indeed Patients D.E. and M.V.D.H. were sensitive at luminance levels as low as 20 cd/m^2.

Discussion. The failure of patients to respond to a grating with uniform brightness and strong colour contrast is of interest given the recent evidence for separation of colour and form processing by the visual system (*see* Gregory, 1977).

There is some evidence to suggest that the Y system is not colour coded (Gouras, 1969) and the present results may arguably be cited as evidence consistent with a trigger involving the Y system. Such an interpretation is, however, highly speculative. Red light excites not only red-sensitive cones but also to a lesser extent green-sensitive cones. The converse is true for green light. There is thus a physical limit for the amount of excitation that a colour contrast grating can provide (File and Mollon, 1976) and this limit is doubtless considerably less than that for a grating with brightness contrast (*see* Study 8). The limit may account for the absence of any convulsive response to isoluminant gratings.

Study 4. Checkerboards v. Gratings

Wilkins, Andermann and Ives (1975) created a series of patterns of checks in which the check width remained constant while the height increased. They found that the probability of the pattern inducing paroxysmal EEG activity increased linearly with the logarithm of the check length/width ratio; the more the checks approximated a grating the greater the likelihood of paroxysmal activity. Subsequently a number of studies have shown that gratings are more epileptogenic than checkerboards. In the course of an investigation of the mechanisms of television epilepsy we presented a series of photosensitive patients with horizontal and vertical square-wave gratings (spatial frequency of 2 cycles/degree) and a checkerboard (check width 15′). Both patterns were 11 degrees square in outline and had a luminance of 2000 cd/m^2 and a contrast of about 0·9. They were either stationary, or vibrated through one half-cycle of the pattern at frequencies of 10, 15, 18 and 25 Hz. For the patient sample as a whole, stripes were more epileptogenic (Darby, Binnie, Harding, Jeavons, Stefansson and Wilkins, 1977).

The difference between stripes and checks is also obtained when the checkerboard is orientated obliquely with its diagonals horizontal and vertical (*see* Study 5) suggesting that the orientation of the pattern is not responsible for the difference between stripes and checks. Orientation of the pattern has also been found to play little, if any, role in the function relating probability of paroxysmal activity to check length/width ratio. Patient M.T., who was also the subject of Wilkins, Andermann and Ives' study, was retested one year after the original experiments were performed. On this occasion the patterns though similar in form were circular in outline. They subtended 16 degrees with a check width of 8′ and were orientated obliquely. The patterns were presented at a viewing distance of 57 cm, according to the standard procedure, a total of six times each. The incidence of paroxysmal EEG activity is shown as 'Session 3' in fig. 3 which also includes Wilkins, Andermann and Ives' original data for comparison. The new data are more noisy than those previously obtained, doubtless because of the small number of trials, but the shape of the function is essentially similar.

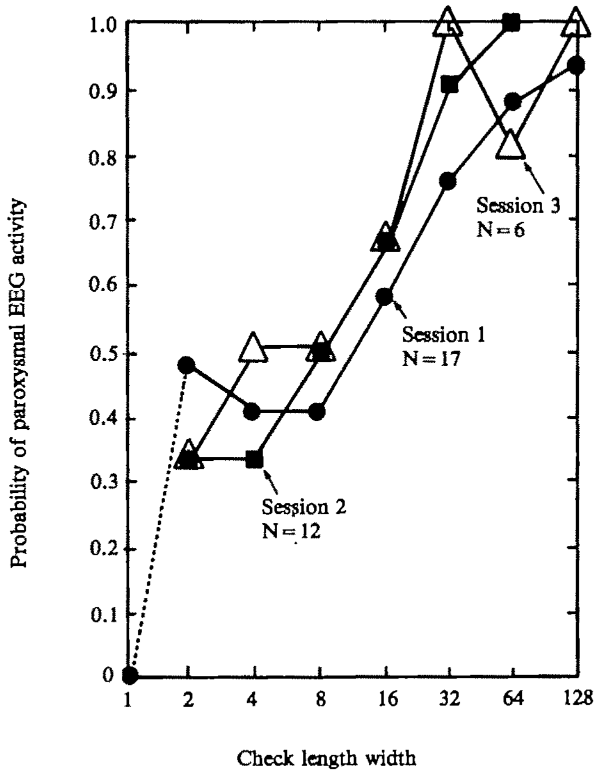

FIG. 3. Probability of paroxysmal EEG activity as a function of check length/width ratio.

Discussion. The increase in the probability of paroxysmal activity with the length of line contour is difficult to interpret in terms of a trigger confined to the LGN where the cells have circular receptive fields, and suggests instead a trigger involving cells with linear receptive fields (Hubel and Wiesel, 1968). Relative to a striped pattern, a checkerboard stimulates such cells ineffectively, but unlike a striped

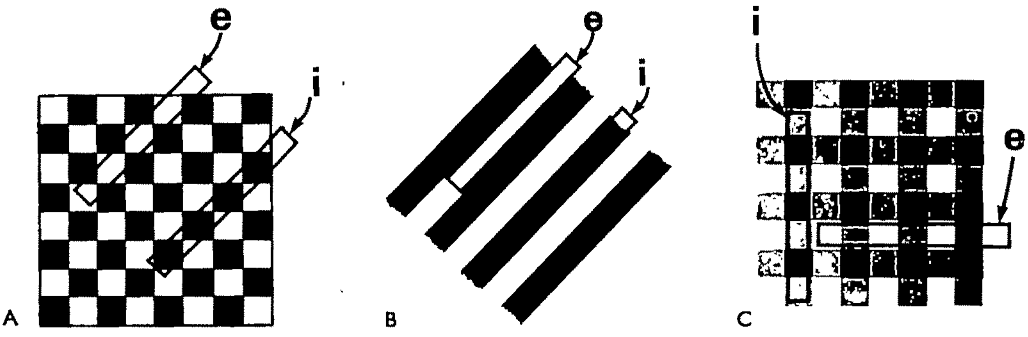

FIG. 4. Stimulation of cells with linear receptive fields and excitatory (e) or inhibitory (i) receptive field centres by A, a checkerboard, B, an oblique square-wave grating and C two superimposed square-wave gratings, one vertical and the other horizontal.

pattern it stimulates cells tuned to a variety of different orientations, particularly those parallel to the diagonals of the checks. Fig. 4A illustrates how a cell with an on-centre and off-surround (e) will be excited by the diagonal of a checkerboard. The mean illumination within the excitatory centre of the cell is greater than that in the surround and so the cell is caused to fire. An exactly analogous process occurs for cells with off-centres (i). The degree of excitation of cells tuned to one particular orientation can never be as great for a checkerboard as for a grating consisting of stripes of similar contrast and appropriate orientation, because in a grating the boundaries of pattern contrast correspond to the borders of the receptive field (*see* fig. 4B). But a grating, unlike a checkerboard, can only excite cells tuned to one particular orientation. Thus a checkerboard differs from a grating in two important respects: first it stimulates cells tuned to a variety of different orientations and second, it stimulates each orientation system relatively ineffectively. The finding that checkerboards and checkerboard-like stimuli were less effective at eliciting paroxysmal activity may have resulted either because cells were stimulated ineffectively or, conceivably, because of some complex 'inhibitory' interaction between cells tuned to different orientations.

To separate the effects of stimulation of several orientations from those of the effectiveness of that stimulation, the fifth study used patterns in which the number of orientations stimulated was allowed to vary while the effectiveness of stimulation in any one particular orientation remained constant.

Study 5. Effects of Mixing Gratings

Patterns were produced by adding to an image of a grating either an image of a diffuse field with the same mean luminance or an image of another grating, similar to the first in every respect except orientation. Fig. 4C illustrates schematically the result of superimposing the images of two orthogonal gratings. Such a stimulus should excite more cells than the stimulus obtained by adding a diffuse field to a grating simply because it contains twice as much modulation of light. As can be seen, the pattern will stimulate cells with linear receptive fields orientated along both a vertical and a horizontal axis. Cells with differently orientated linear receptive fields will not be stimulated so effectively.

Stimuli were produced by two methods. One involved the physical superimposition of the images from two projectors (Experiment (i)). As a result the contrast of the images varied with the ambient illumination. The second method (Experiment (ii)) used a semisilvered mirror to achieve the optical superimposition of the images of two fields, one viewed by transmission through the mirror, the other by reflection from its surface. In both cases the mean luminance of the two component fields was equal.

The two patients who took part in this study were selected on the basis that they were sensitive to patterns in a variety of orientations.

Study 5, Experiment (i)

Method. Patient K.O. was seated in a well-lit room in front of a 25 cm square white card at a viewing distance of 104 cm. Two 35 mm slide projectors matched for luminous intensity were mounted behind the patient so that their images filled the card. Each projector could display a slide of a square-wave grating or a slide containing a neutral density filter with the same average transmittance. When both projectors were brought to focus on the card, one providing a grating and the other a diffuse uniform field, the image of the grating had a spatial frequency of 1·6 cycles/degree, a mean luminance of 90 cd/m^2 and a contrast of 0·2. Two such gratings were used, one horizontal and one vertical. Their effects were compared with those of a third stimulus obtained by overlapping the images of a vertical and a horizontal grating, one from each projector. There was little change in mean luminance at pattern onset or offset.

Twelve series of 3 to 11 presentations, each separated by at least 10 s were given. One stimulus was presented throughout each series and the series alternated between the two superimposed gratings and one or other of the two single gratings chosen at random.

Results. The incidence of paroxysmal EEG activity in response to the vertical grating was 8/19 trials (42 per cent) as compared with 12/22 (54 per cent) in response to the horizontal grating. The incidence in response to the two superimposed gratings was 8/41 trials (19 per cent), significantly lower than for the single gratings ($\chi^2(1) = 6{\cdot}56$, $P < 0{\cdot}02$).

Study 5, Experiment (ii)

Apparatus. A box measuring 30 × 30 × 30 cm contained a diagonal semisilvered mirror positioned so that when the patient looked through an aperture in the front of the box he saw not only the back of the box (visible by light transmitted through the mirror) but also one of the sides (visible by reflection). The two visible surfaces each contained a central circular aperture, 10 cm in diameter, optically superimposed, subtending 15 degrees. A stimulus field mounted 9 cm behind each aperture was illuminated by 10 'festoon' tungsten bulbs. The bulbs were arranged in a ring concentric with the aperture but 4 cm greater in diameter, mounted between the aperture and the stimulus field and thus hidden from view. The two rings were wired in series. Two sheets of polarizer with axes of polarization orthogonal to one another, one across each circular aperture, enabled the two simulus fields to be mixed in varying degrees depending upon the orientation of a third polarizer placed between the patient and the mirror.

Procedure. Ten types of pattern stimuli were presented and they are shown schematically in Table 2.

TABLE 2. INCIDENCE OF PAROXYSMAL EEG ACTIVITY IN RESPONSE TO MIXED PATTERNS

Stimulus	Field 1	Field 2	Incidence of paroxysmal activity	%
a			0/9	0
b		●	1/9	11
c		●	1/9	11
d			0/9	0
e			2/9	22
f			5/9	55
g	●		4/4	100
h			3/5	60
i		Occluded	5/9	55
j		Occluded	0/9	0

Stimuli a–e were produced by a vertical square-wave grating (3·4 cycles/degree, contrast 0·6) in one field, and a similar grating in the other with orientation 90, 45, 22, 11 and 6 degrees to the vertical respectively. For stimuli f, g and h, a vertical, oblique, or horizontal grating was shown in one field, while the other contained a uniform grey patch with the same mean reflectance as the grating. For all the above stimuli (stimuli a–h) the third polarizer was orientated with its axis of polarization at 45 degrees to the other two so that the two fields were mixed in equal proportion. As a result the contrast of the single grating was 0·3. The remaining stimuli (i–j) were produced by orientating the polarizers so that one field was occluded. The other field contained a vertical grating (stimulus i) or an oblique checkerboard with check width 9′ (stimulus j). The use of polarizers ensured that for every stimulus the mean luminance remained constant. Stimulus onset and offset were associated with a considerable change in luminance because the patterns were not illuminated during the interval between presentations.

Patient L.D. acted as subject. After a few initial trials it was established that at a mean luminance of 34 cd/m^2 the patient was sensitive to some patterns and not to others, and this luminance was used for the remainder of the experiment. Presentations lasted a maximum of 10 s and the intertrial interval was approximately 20 s although the patient was given a rest of several minutes between blocks of ten trials. In order to limit the occurrence of generalized spike and wave activity stimuli g and h were omitted halfway through the session.

Results. The incidence of paroxysmal activity for mixed gratings (stimuli a–e) was 4/45 (*see* Table 2). This incidence was significantly lower than that for single gratings, whether full contrast (stimulus i, $P<0{\cdot}01$, Fisher exact probability test) or reduced contrast (stimuli f–h, $P<0{\cdot}001$, Fisher exact probability test). The checkerboard was significantly less epileptogenic than the single full-contrast gratings ($P<0{\cdot}05$, Fisher exact probability test), confirming the results obtained earlier with patient M.T.

Discussion. Even though the superimposed gratings modulated twice as much light as single gratings they were less epileptogenic. This finding suggests the hypothesis that cells with orientation selectivity are involved in the triggering of paroxysmal activity. Such a hypothesis would be quite consistent with the finding of Study 2 that selective sensitivity to some grating orientations is rare and possibly attributable to astigmatism; presumably large numbers of orientationally selective cells with a wide variety of orientation tunings are involved.

The origin of the apparent 'inhibitory' interaction between the two gratings is difficult to interpret. While it is true that most intracortical connections are inhibitory, recent evidence would suggest that this inhibition is maximal when the component orientations of a complex stimulus are similar (Fries, Albus and Creutzfeldt, 1977). No effects of similarity were apparent in Experiment (ii).

Whatever the interpretation of the 'inhibitory' interaction, the results of the present study indicate that the difference between checks and gratings discussed in Study 4 is at least partly due to the fact that a checkerboard stimulates cells tuned to a variety of different orientations. The effects of binocular rivalry, now to be described, may also be due to the different component orientations of a pattern presented in rivalry.

Study 6. Effects of Binocular Rivalry

Wilkins *et al.* (1975) used a stereoscope to present horizontal or vertical gratings separately to the two eyes. They found that the probability of paroxysmal activity was greater when both eyes saw similarly orientated gratings than when the orientations were different for each eye. This finding has now been replicated with two patients, D.E. and H.V.D.

Procedure. A stereoscope with a binocular field subtending 15 degrees was used to present prints of square-wave gratings with a spatial frequency of 2 cycles/degree and mean luminance of approximately 20 $\mathrm{cd/m^2}$. Horizontal and vertical gratings were presented to the right and left eyes in all four of the possible combinations, according to the standard procedure. Maximum presentation time was 12 s.

TABLE 3. INCIDENCE OF PAROXYSMAL EEG ACTIVITY IN RESPONSE TO STEREOSCOPIC PATTERNS

Left eye	*Right eye*	*D.E.*	*H.V.D.*
⦀	⦀	5/9 (55%)	8/14 (57%)
≡	≡	8/8 (100%)	15/19 (79%)
⦀	≡	2/7 (29%)	8/16 (50%)
≡	⦀	4/9 (44%)	7/18 (39%)

Results. Table 3 shows the incidence of paroxysmal activity. Patterns that fused were significantly more epileptogenic than those that were in rivalry ($P < 0{\cdot}05$ in both cases, Fisher exact probability tests).

Discussion. Patterns that fuse in binocular vision are more epileptogenic than those that do not. This effect could be due to the greater stimulation of binocular cells by patterns that fuse (Wilkins *et al.*, 1975) but it is also possible that an interaction between the two orientations reduced patients' sensitivity in a manner analogous to that of the previous study (Study 5), quite independently of any binocular effect. Whichever was the case, the results are difficult to reconcile with a trigger confined to the LGN because geniculate cells are monocular and they are not orientation selective. Cells in the superior colliculus are binocular, but few are orientation selective (Goldberg and Wurtz, 1972). It is only in the cortex that the majority of cells are both binocular and orientation selective. It would therefore be interesting to assess the possible role of binocular cells independently of the confounding effects of orientation. For this reason the following study investigated the effects of interocular phase on the response to diffuse flicker.

Study 7. Effects of Counterphase Interocular Flicker

As Sherrington (1904) observed 'Ordinarily when the binocular gaze is directed upon an object intermittently illuminated, successive phases of illumination affect the corresponding areas of the two retinae synchronously. The question rises, will the rate of repetition necessary for visual fusion of the successive light phases be altered if those phases fall upon corresponding retinal points not synchronously but alternately?' He found that 'the light phases at the one eye practically do not . . . interfere or combine at all with the coincident dark phases at the other' and concluded that the 'right and left corresponding retino-cerebral points do not when tested by flicker reactions behave as though combined or conjugate to a single mechanism'. Since the majority of pattern-sensitive patients are sensitive not only to pattern but also to a diffuse flickering field (IPS), Sherrington's technique was applied to the induction of paroxysmal EEG activity by flicker in order to assess the contribution of monocular and binocular mechanisms. The probability of paroxysmal activity was plotted as a function of (temporal) frequency and the peak of the resulting 'tuning curve' for monocular flicker compared with that for alternate stimulation of the two eyes.

Apparatus. The light from a frosted 100W tungsten filament bulb passed through a system of prisms and lenses and was brought into Maxwellian view at two lenses, one for each eye. This created a diffuse binocular 8 degree field. The field was bisected by horizontal and vertical lines, 0·6 degrees wide, that formed a fixation cross. Due to the large surface area of the light source, the field remained uniformly illuminated at all head positions permitted by a face mask, and so a bite bar was not needed.

The light path was interrupted near its source by a sectored disc mounted in a plane orthogonal to the light path. The disc rotated about a central axle, belt-driven by an electrostatically screened 6V DC motor at a speed that could be controlled by a rheostat and measured from a magnetic tachometer attached to the axle.

The surface of the disc was covered by a neutral-density filter with a transmission equivalent to that of two type HN 32 polarizers (Polarizers UK Limited) with orthogonal axes of polarization. In two 6 degree sectors of the disc, spaced 180 degrees apart, the neutral filter was replaced by a polarizer. The axes of polarization of the four polarizers were identical. With suitably orientated polarizers placed in front of each eye the disc could be made to produce alternate flashes first to one eye and then the other. The flash duration was, of course, determined by the speed of rotation of the sectored disc, but the pulse to cycle fraction (duty cycle) of stimulation remained constant at 6/180 = 3·3 per cent.

The disc could be slid in and out of the light path whilst it rotated, and when out of the beam its place was taken by a static neutral density filter with approximately the same average transmission as provided by the rotating disc. This allowed sudden onset of modulation with little change in time-averaged luminance. The luminance of the field was 2000 cd/m² for the duration of the flash and 25 cd/m² otherwise. The flicker frequency was sufficient to render the use of an artificial pupil unnecessary. The detail of the alternate eye condition is summarized in fig. 5. The monocular conditions were identical but for the occlusion of one eye.

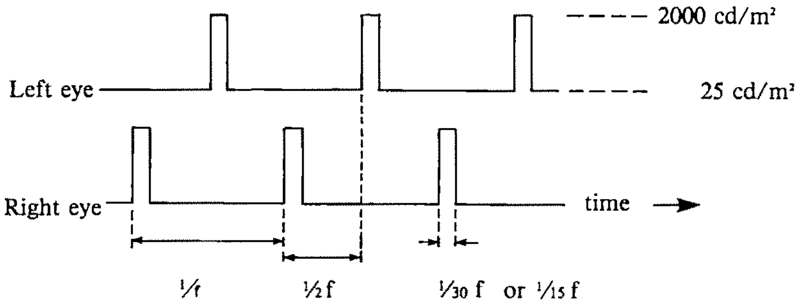

FIG. 5. Parameters of flicker stimulation at frequency f in the alternate eye condition of Study 7.

Procedure. Patient M.T. took part in the study. Like the majority of pattern-sensitive patients she was sensitive not only to patterns but also to diffuse flicker (IPS). She was seated so that her head rested in the face mask and was instructed to look at the centre of the cross. The rotating disc was then slid into the light beam causing the diffuse field to be temporally modulated with a frequency and interocular phase selected according to a schedule in which a 10 s presentation of flicker (terminated if paroxysmal EEG activity appeared) was followed by an interval of at least 20 s. The presentations were grouped so that all the frequencies were tested in random order either once or twice within a block and the patient was allowed to rest between blocks. Blocks of trials under the three conditions of stimulation were ordered within a testing session so that any effects of practice or sensitization would be equated for the three conditions.

The data were collected on three days. On the first two days the flicker had a duty cycle of 3·3 per cent (measured at one eye). On day 1 the data for right eye, left eye and alternate eyes were collected; on day 2 further observations were collected for the alternate eye condition. On the third day the disc was replaced by one with four 6 degree sectors spaced 90 degrees apart, providing a 6·6 per cent duty cycle. Further data were then collected for all three conditions of presentation.

TABLE 4. INCIDENCE OF PAROXYSMAL EEG ACTIVITY AS A FUNCTION OF THE FREQUENCY AND DUTY CYCLE OF MONOCULAR FLICKER AND ALTERNATE INTEROCULAR FLICKER

	Duty cycle	*Flash frequency at one eye (Hz)*							
Eye	*(%)*	*5*	*7·5*	*10*	*15*	*20*	*25*	*30*	*40*
Right	3·3	—	—	0/5	2/5	2/3	—	1/4	—
	6·6	—	—	0/5	1/5	2/5	3/5	1/5	0/5
Left	3·3	—	—	0/4	1/4	5/5	—	4/5	0/4
	6·6	—	—	0/5	1/5	5/5	4/5	3/5	0/5
Alternate	3·3	0/12	1/13	2/25	15/19	7/17	—	—	—
	6·6	—	—	2/10	6/10	5/10	2/10	0/10	—

Results. The incidence of paroxysmal EEG activity under the various conditions of flicker frequency, duty cycle and eye stimulated are shown in Table 4. It can be seen that, for the values used, the effects of duty cycle are negligible compared with those of frequency. For this reason the data for the two conditions of duty cycle have been combined to form the data points shown in fig. 6. The curves in this figure were obtained by fitting the probability of paroxysmal activity at a given frequency, P(A|f), by a three-parameter logit-linear model

$$\text{logit } P(A|f) = \alpha(f-\mu)^2+\gamma$$

where μ is the frequency at which the probability of paroxysmal activity is greatest, α determines the 'sharpness' of the peak and γ the overall height of the curve. The model is a natural extension of standard dosage-response curve-fitting methods (Nimmo-Smith, in preparation).

Maximum likelihood solutions were obtained for different values of μ, allowing the other two parameters, α and γ, to attain their optimum. Iterative techniques were then used to obtain the optimum value of μ. In other words the value of μ giving the best fit regardless of the other parameters of the model was obtained (Nimmo-Smith, in preparation).

The values of μ for monocular stimulation were very similar: 22·4 Hz for the right eye (95 per cent confidence limits: 19·5, 26·0) and 23·5 Hz for the left (confidence limits: 22·5, 25·5). The value of μ for stimulation of alternate eyes was significantly lower: 17·1 Hz (confidence limits: 15·5, 18·5). Lest it be argued that the above curve-fitting procedures beg too many questions about the physiological nature of the data they describe, it is worth noting that the incidences of paroxysmal activity in response to monocular stimulation and stimulation of alternate eyes differ significantly at the 15, 20, 25 and 30 Hz points ($P < 0{\cdot}05$, Fisher exact probability tests).

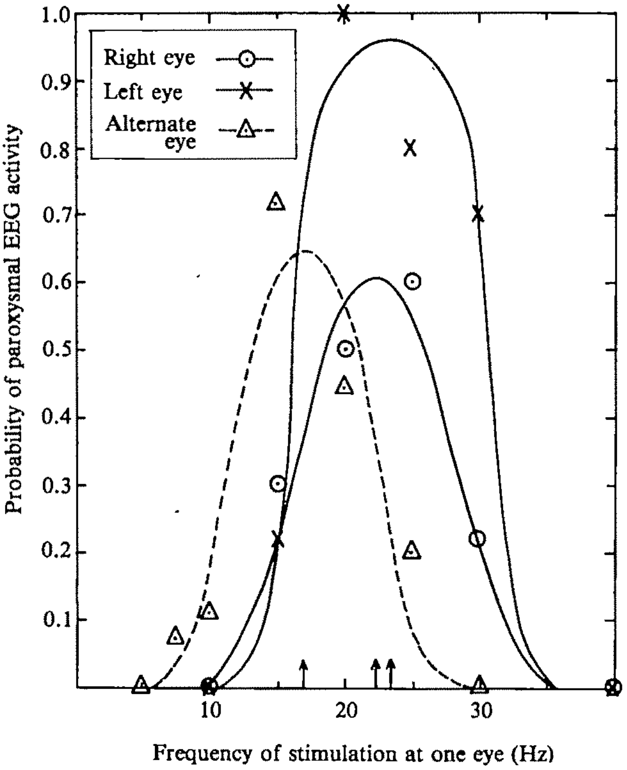

FIG. 6. Probability of paroxysmal EEG activity as a function of the frequency of monocular flicker and alternate interocular flicker.

Discussion. The results of Study 7 clearly implicate binocular interaction in the induction of paroxysmal activity by flicker, an interaction that occurs independently of orientation. If there were no binocular interaction the peak of the tuning curve for monocular and alternate eye stimulation should have been identical. If the interaction were complete the peak for alternate eye stimulation should have been half that for monocular (that is, about 11·5 Hz). The result in fact obtained is evidence for a partial interaction between the two eyes, as would occur if populations of (predominantly) monocular and (predominantly) binocular cells were stimulated. Simple models of the possible interaction between monocular and binocular components would predict a bimodal tuning curve for alternate eye stimulation. The data are insufficient to distinguish a bimodal from a unimodal curve.

If the mechanisms for the induction of paroxysmal activity by flicker are similar to those of pattern induction, and there is at present no reason to suppose that they are not, the findings of the present experiment may be combined with those of the other experiments described so far. The picture that obtains is entirely consistent with the hypothesis of a seizure trigger in the striate cortex, where the majority of cells are orientation selective and have a degree of binocularity. Neurons in the LGN are monocular and although there is evidence of some binocular interaction in the cat (*see* Sanderson, Darian-Smith and Bishop, 1969) which may arise from corticofugal fibres (Schmielau and Singer, 1977) the interaction is not extensive. It is therefore unlikely that a trigger confined to the LGN could have produced the considerable interaction between the two eyes observed in fig. 6. A subcortical pathway from LGN to the diffuse thalamic system is therefore unlikely.

The next experiments attempt to address the question as to how the probability of paroxysmal EEG activity relates to the general level of excitation that may be assumed to be occurring as a result of pattern stimulation.

Study 8. Effects of Brightness Contrast

In cat cortex the rate at which cells fire is determined by the contrast across the boundaries of the receptive fields. The rate of firing increases with increasing contrast up to contrasts of between 0·1 and 0·3, at which most cells have either saturated or have begun to do so (D. J. Tolhurst, J. A. Movshon and I. D. Thompson, personal communication). If the probability of paroxysmal activity shows a similar relationship to contrast it might be reasonable to hypothesise a direct relationship between the general level of activation in the cortex and the paroxysmal activity that results.

Study 8, Experiment (i)

Procedure. Two projectors were mounted side by side so that their beams were coincident on a distant screen. One projector contained a slide of a vertical square-wave grating; the other was used to provide a diffuse uniform field. A mask with a central circular aperture was mounted parallel to the object plane of each projector but slightly displaced so that the superimposed images of the grating and field had a common but indistinct circular boundary. The beams from the projectors each passed through a polarizer, and the two polarizers were mounted rigidly with orthogonal axes of polarization. The beams emerging from the polarizers were adjusted to have the same luminous flux. The beams then passed through different sections of a large disc of polarizer that could be rotated in a plane perpendicular to the beams. As it rotated the angle between the axes of polarization of the disc and the two stationary polarizers changed by an exactly equivalent amount, the intensity of one beam being reduced as the other increased. Thus by rotating the disc the contrast of the image of the grating on the screen could be manipulated whilst the mean luminance remained constant.

When the polarizer was orientated to provide an image of maximum contrast, the actual contrast of the image was measured by taking several readings with a spot photometer (Salford Electrical Instruments Ltd). Lower contrast levels produced by rotating the polarizers were calculated on the basis of the theoretical reduction in maximum contrast. Contrast values are therefore limited in accuracy to ±5 per cent.

The grating had a mean luminance of 55 cd/m², a spatial frequency of 2 cycles/degree and a total subtense of approximately 35 degrees. Patient M.V.D.H. was seated 57 cm from the screen and instructed to fixate a 1 cm black square attached to the screen at the centre of the concentric circular overlapping images from the two projectors. The gratings were presented by rapidly increasing the contrast from zero to one of the four values: 0·08, 0·28, 0·41 and 0·52. Pattern presentations were not, therefore, accompanied by any change in mean luminance.

Results. For the four levels of contrast compared (0·08, 0·28, 0·41 and 0·52) the incidence of paroxysmal EEG activity was 0/5 (0 per cent), 2/16 (13 per cent), 9/13 (69 per cent) and 13/14 (93 per cent) trials respectively. The results are shown in fig. 7.

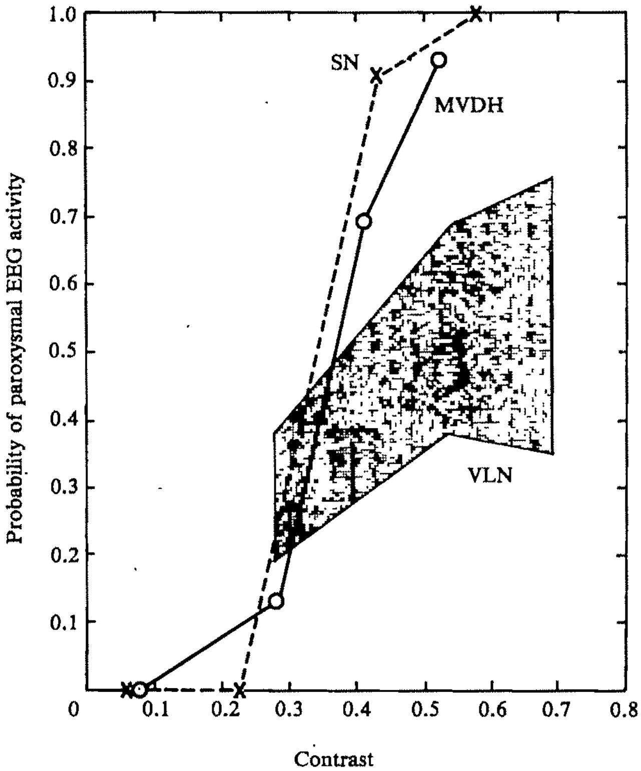

FIG. 7. Probability of paroxysmal EEG activity as a function of the contrast of a square-wave grating.

Study 8, Experiment (ii)

Procedure. The procedure was similar to that for Experiment (i) except that the following levels of contrast were compared: 0·28, 0·54 and 0·69. Patient V.L.N. took part.

Results. The paroxysmal activity was difficult to assess. The proportion of unequivocally positive trials was 3/16 (19 per cent), 5/13 (38 per cent), 6/17 (35 per cent) for the three levels of contrast respectively. If equivocal trials are included as positive the proportions are 6/16 (38 per cent), 9/13 (69 per cent) and 13/17 (76 per cent). The shaded area in fig. 7 is bounded by these proportions.

Study 8, Experiment (iii)

Procedure. The grating was viewed from a distance of 114 cm at which distance it had a spatial frequency of 4 cycles/degree and subtended about 16 degrees. The mean luminance was 100 cd/m². Patient S.N. took part in the experiment. The following contrasts were compared using the usual randomized procedure: 0·06, 0·23, 0·43 and 0·58.

Results. The incidence of paroxysmal activity was 0/10, 0/11, 10/11 and 11/11 for the four levels of contrast respectively.

Discussion. Fig. 7 provides a summary of the results of the three experiments. It can be seen that the increase in the probability of paroxysmal activity shows a very steep ascent for values near 0·3. This sudden ascent does not mirror the progressive increase in firing rate with increasing contrast observed in cat cortex by D. J. Tolhurst, J. A. Movshon and I. D. Thompson (personal communication). If the paroxysmal activity is triggered in the cortex, and if the response of the human cortex to pattern contrast is similar to the cat's, then the present results would suggest that the probability of paroxysmal activity is not directly related to the general level of excitation. Rather the probability appears to increase abruptly only when the majority of cortical cells are firing at or near saturation. These are tentative inferences and further evidence is desirable. A more direct way to examine the effects of the level of excitation was employed in the next study in which the number of cells stimulated was varied by manipulating pattern size.

Study 9. Effects of Pattern Size

Procedure. Prints of vertical square-wave gratings were prepared with a spatial frequency of 2 cycles/cm, contrast 0·78, circular in outline with radii of 2, 3, 4·5, 6, 8, 10, 12·5, 15 and 24 cm. A red fixation point 1 mm in diameter was placed at the centre of each pattern, on the boundary between a black and a white stripe. The patterns were mounted on grey rods and could be placed at the centre of a vertical grey screen which had the same mean reflectance as the pattern. The screen was illuminated by two projectors mounted either side of the patient and the patterns and screen had a mean luminance of 600 cd/m². The patient was usually seated at a distance of 57 cm from the screen so that the grating had a spatial frequency of 2 cycles/degree. The patients were instructed to fixate the red dot when the pattern was placed before them. Only one patient (H.V.D.) had difficulty complying with the instructions. All patients were observed during the presentation of the patterns, and trials accompanied by an obvious deviation of gaze were eliminated. The patterns were presented in ascending order of size until paroxysmal EEG activity appeared, and patterns near the threshold size were then repeatedly presented in random order. Maximum presentation time was 10 s with a minimum interval between presentations of 10 s.

Results. Figure 8 shows the way in which the probability of paroxysmal activity varied with the size of pattern. The mean number of observations per point averaged 10 with a minimum of 7. Points connected by a broken line were obtained using patterns with a spatial frequency of 4 cycles/degree. In the case of the most sensitive patient (D.E.) the viewing distance was increased to 114 cm because at 57 cm there were no patterns to which she failed to respond. In the case of patient M.W. the 4 cycles/degree point was obtained at a viewing distance of 57 cm using a 4 cycles/cm pattern. (Note that the 2 cycles/degree and 4 cycles/degree patterns with a radius of 2 degrees contained four and eight cycles respectively; Kelly, 1975.)

One patient, H.V.D., was tested on two occasions. On one occasion the resulting EEG contained spontaneous paroxysmal EEG activity (H.V.D. 1); on the other it did not (H.V.D. 2). Patient G.F. also had spontaneous paroxysmal activity. In both cases the incidence of this activity indicated that in a period of 10 s duration (the presentation period) the probability of observing paroxysmal activity was about 0·3.

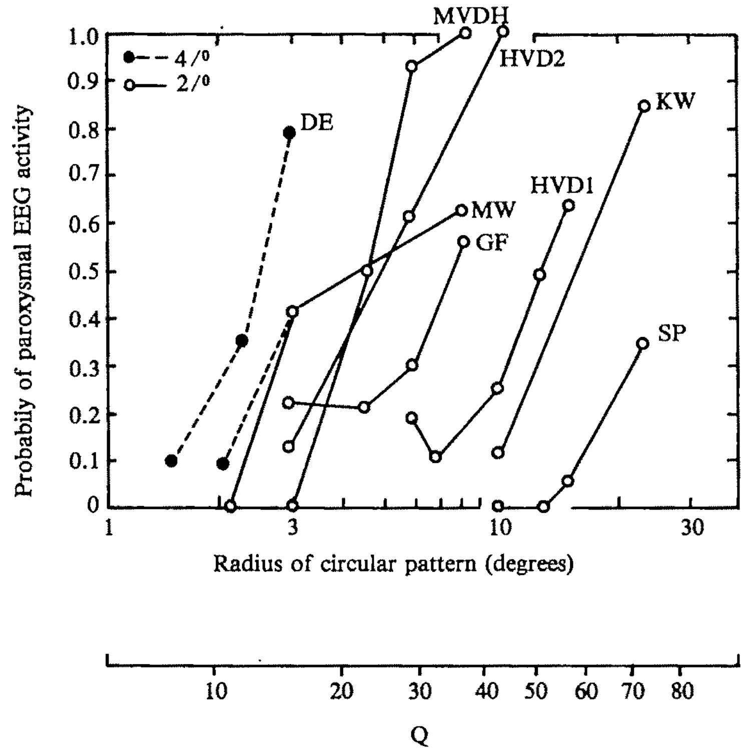

FIG. 8. Probability of paroxysmal EEG activity as a function of the subtense of a square-wave grating, contrast 0·78, mean luminance 600 cd/m², spatial frequency 2 or 4 cycles/degree, as shown.

Discussion. Drasdo (1977) has calculated the percentage surface area of striate cortex (Q) corresponding to a concentric region of visual space. He finds

$$Q = 100\,(1-\exp\,(-0{\cdot}0574\theta))$$

where θ is the angular radius. Since the density of cortex is uniform (Daniel and Whitteridge, 1961), Q may be taken to be the proportion of cortical cells available for analysis of the area of the visual field determined by θ. The scale for Q is shown beneath that for pattern radius in fig. 8. Any pattern will stimulate a certain proportion of the cells available for the area of visual field that it covers. The proportion of the available cells that are actually stimulated will vary with attributes of the pattern such as its spatial frequency. A 2 cycles/degree grating will not stimulate the same proportion of cells in all areas of the visual field given the increase in receptive field size with increasing eccentricity. If the data in fig. 8 are replotted against Q the curves decrease in slope as the x-intercept increases. This may be interpreted as indicating that the probability with which paroxysmal activity is evoked by a pattern is lawfully related to the number of cells that the pattern activates. The decrease in the slope of the curves with increasing intercept may be attributed to a reduction in the proportion of available cells actually stimulated by a 2 cycles/degree pattern as more of the periphery of the visual field is involved. This being the case, the simplest interpretation of the present data would be that paroxysmal activity occurs when a given number of visual cells are activated, and subsequently increases in probability with the number of cells activated in excess of this threshold.

If the probability of paroxysmal activity is indeed a simple function of the number of cells firing in excess of threshold it should not matter which areas of striate cortex are stimulated. An annular grating should be as effective as a complete grating provided it stimulates the same number of cells. Experiments along these lines are being conducted at the time of writing and preliminary findings suggest that the probability of paroxysmal activity is indeed independent of retinal location stimulated.

The results of Study 9 are preliminary in many respects. For a meaningful comparison of slopes more data points on each curve are required. However, the data are sufficient to demonstrate three important facts:

(1) The increase in the probability of paroxysmal activity with increasing pattern size is extremely steep.

(2) Patients have very different curves. This point is of considerable interest given the remarkable degree of consistency between patients as regards the effects of spatial frequency, colour contrast, checkerboards, binocular rivalry and brightness contrast. It suggests that whereas the manipulations involved in the majority of experiments described in this paper affect large numbers of neurons, manipulations of pattern size affect relatively few.

(3) Large patterns may be necessary to detect pattern sensitivity. It will be suggested elsewhere (Wilkins, Darby and Binnie, in preparation) that the routine

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testing for pattern sensitivity may be of clinical value in the assessment of patients referred with suspected epilepsy. There are three grounds for supporting this position. First, some 50 per cent of patients sensitive to IPS are also sensitive to patterns; secondly, pattern sensitivity cannot reliably be determined from characteristics of the response to IPS; thirdly, a pattern-sensitive patient is liable to attacks induced by the large number of striped patterns in the modern urban environment. It might be argued that a pattern subtending 48 degrees has no counterpart in the normal environment and is therefore an unnecessarily provocative stimulus with which to assess sensitivity to environmental pattern. Such an argument ignores the fluctuations in a patient's sensitivity that can occur (*see* H.V.D., fig. 8).

The differences between patients have a theoretical significance in terms of the numbers of neurons needing to be excited in order for paroxysmal activity to occur. The use of patterns with a variety of sizes may therefore provide a useful model for assessing the effects of anticonvulsants on photosensitivity.

GENERAL DISCUSSION

Wilkins, Andermann and Ives (1975), in their discussion of the nature and locus of the trigger mechanism in pattern-sensitive epilepsy, concluded that seizures appeared to be triggered in the striate cortex, possibly by the firing of complex cells. The results of the present series of studies have replicated their findings with other pattern-sensitive patients, and provided further data consistent with the notion of a cortical locus for the trigger mechanism. The results do not, however, rule out a trigger in the superior colliculus.

Wilkins *et al.* used the evidence for binocular involvement in the trigger mechanism to argue that binocular neurons (for example, complex cells) were involved. This hypothesis is still tenable but, given the present evidence that the trigger arises from the mass action of cells, a more parsimonious hypothesis is simply that paroxysmal EEG activity arises when neural activation reaches a threshold level; the activation resulting from cells of a wide variety of types. The mass action of cells with varying degrees of binocularity, such as are known to occur in the striate cortex, some responding more to one eye, some more to the other, would give effects that could not, on the basis of present evidence, be distinguished from those of predominantly binocular cells.

Given the present evidence for mass action it is intriguing to speculate whether the mass action occurs within orientation columns or between them. Recent evidence from penicillin foci in cat cortex would suggest that the action is confined to cells within a column (Gabor and Scobey, 1977).

The relation between flicker-induced and pattern-induced paroxysmal activity appears to be a close one. Patients who are more sensitive to one form of stimulation are more sensitive to the other (Wilkins, Darby and Binnie, in preparation). It is quite possible that intermittent temporal stimulation of retinal cells by the microsaccades that occur during fixation may be necessary for patterns to induce paroxysmal activity; such movements are certainly necessary for continuous form perception (Riggs, Ratliff, Cornsweet and Cornsweet, 1953). This is not to say that intermittent stimulation of the retina is a sufficient explanation of the trigger mechanism: the seizure discharge is most unlikely to occur solely as the result of abnormal neural activity at the level of the retina (Green, 1969). Whatever the role of such retinal intermittence, it cannot impair the inference made from Study 7 which, in implicating a considerable degree of binocular interaction in the seizure trigger independently of any possible contribution from eye movements, makes a seizure trigger confined to the lateral geniculate nucleus unlikely. In the present paper no attempt has been made to disentangle spatial from temporal factors in the induction of paroxysmal activity by patterns. It remains to be seen whether spatial attributes alone are sufficient.

SUMMARY

The capacity of striped patterns (square-wave gratings) to induce paroxysmal EEG activity in a group of pattern-sensitive epileptic patients is shown to depend on:

1. The spatial frequency of the pattern. The optimum spatial frequency lies between 1 and 4 cycles/degree in every patient tested.

2. The orientation of the pattern. Although, for the patient group as a whole, no one orientation is consistently more likely to induce paroxysmal activity than any other, the responses of individual patients can show marked orientation selectivity.

3. The brightness contrast of the pattern. The probability of paroxysmal EEG activity increases dramatically as contrast is increased from 0·2 to 0·4. Red/green gratings at isoluminance fail to induce paroxysmal activity.

4. The size of the pattern. There is considerable variation between patients in the subtense of a centrally-fixated circular pattern necessary to induce paroxysmal activity with a given probability. However, for every patient an increase in the probability of paroxysmal activity from near zero to near unity is effected by an increase in the angular subtense of the pattern by a factor of two.

Patterns other than square-wave gratings are capable of inducing paroxysmal activity but, in general, patterns that stimulate more than one orientation system are less epileptogenic.

The above findings are compatible with the hypothesis of a seizure trigger in the striate cortex and are incompatible with a trigger confined to the lateral geniculate nucleus of the thalamus. Further evidence against a geniculate trigger is obtained from an investigation of the response of a pattern-sensitive patient to a diffuse (unpatterned) flickering field in which it is shown that the effects of counterphase interocular flicker implicate binocular mechanisms.

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REFERENCES

Bickford, R. G., Daly, D. and Keith, H. M. (1953) Convulsive effects of light stimulation in children. *American Journal of Diseases of Children*, **86**, 170-183.

Calvin, W. H. (1975) Generation of spike trains in CNS neurons. *Brain Research, Amsterdam*, **84**, 1-22.

Campbell, F. W. and Robson, J. G. (1968) Application of Fourier analysis to the visibility of gratings. *Journal of Physiology, London*, **197**, 551-566.

Chatrian, G. E., Lettich, E., Miller, L. H. and Green, J. R. (1970) Pattern-sensitive epilepsy, Part 1. An electrographic study of its mechanisms. *Epilepsia*, **11**, 125-149.

Daniel, P. M. and Whitteridge, D. (1961) The representation of the visual field on the cerebral cortex in monkeys. *Journal of Physiology, London*, **159**, 203-221.

Darby, C. E., Binnie, C. D., Harding, G. F. A., Jeavons, P. M., Stefansson, S. F. and Wilkins, A. J. (1977) Television epilepsy and pattern sensitivity. *Electroencephalography and Clinical Neurophysiology*, **43**, 577.

Drasdo, N. (1977) The neural representation of visual space. *Nature, London*, **266**, 554-556.

File, S. E. and Mollon, J. D. (1976) Book Reviews. *Quarterly Journal of Experimental Psychology*, **28**, 691-692.

Fries, W., Albus, K. and Creutzfeldt, O. D. (1977) Effects of interacting visual patterns on single cell responses in cat's striate cortex. *Vision Research*, **17**, 1001-1008.

Gabor, A. J. and Scobey, R. P. (1977) Epileptogenicity and the cortical column. *Electroencephalography and Clinical Neurophysiology*, **43**, 461.

Goldberg, M. E. and Wurtz, R. H. (1972) Activity of superior colliculus in behaving monkey. I. Visual receptive fields of single neurons. *Journal of Neurophysiology*, **35**, 542-559.

Gouras, P. (1969) Antidromic responses of orthodromically identified ganglion cells in monkey retina. *Journal of Physiology, London*, **204**, 407-419.

Green, J. B. (1969) Photosensitive epilepsy: the electroretinogram and visually evoked response. *Archives of Neurology, Chicago*, **20**, 191-198.

Gregory, R. L. (1977) Vision with isoluminant colour contrast. 1. A projection technique and observations. *Perception*, **6**, 113-119.

HUBEL, D. H. and WIESEL, T. N. (1968) Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, London*, **195**, 215–243.

JEAVONS, P. M. and HARDING, G. F. A. (1975) *Photosensitive Epilepsy*. London: Heinemann.

KELLY, D. H. (1975) How many bars make a grating? *Vision Research*, **15**, 625–626.

MELDRUM, B. S. and BALZAMO, E. (1972) Epilepsy in the photosensitive baboon, *Papio papio*, and drugs acting on cerebral GABA and serotonin mechanisms. In: *Medical Primatology 1972*. Edited by E. I. Goldsmith and J. Moor-Jankowski. Karger: Basel.

MERLIS, J. K. (1970) Proposal for an international classification of the epilepsies. *Epilepsia*, **11**, 114–119.

NAQUET, R., CATIER, J. and MENINI, C. (1975) Neurophysiology of photically induced epilepsy in *Papio papio*. In: *Advances in Neurology*. Edited by B. S. Meldrum and C. D. Marsden. New York: Raven Press, Vol. 10.

NIMMO-SMITH, I. Models for estimating peak sensitivities with all-or-nothing observations. In preparation.

PARKER, D. M. and SALZEN, E. A. (1977) The spatial selectivity of early and late waves within the human visual evoked response. *Perception*, **6**, 85–95.

RIGGS, L. A., RATLIFF, F., CORNSWEET, J. C. and CORNSWEET, T. N. (1953) The disappearance of steadily fixated visual test objects. *Journal of the Optical Society of America*, **43**, 495–501.

SANDERSON, K. J., DARIAN-SMITH, I. and BISHOP, P. O. (1969) Binocular corresponding receptive fields of single units in the cat dorsal lateral geniculate nucleus. *Vision Research*, **9**, 1297–1303.

SCHMIELAU, F. and SINGER, W. (1977) The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus. *Brain Research, Amsterdam*, **120**, 354–361.

SHERRINGTON, C. S. (1904) On binocular flicker and the correlation of activity of 'corresponding' retinal points. *British Journal of Psychology*, **1**, 26–60.

SOSO, M. J. and LETTICH, E. (1978) Pattern-sensitive epilepsy: spatial frequency channels demonstrated by visual psychophysics. *Electroencephalography and Clinical Neurophysiology*. In press.

STEFANSSON, S. B., DARBY, C. E., WILKINS, A. J., BINNIE, C. D., MARLTON, A. P., SMITH, A. T. and STOCKLEY, A. V. (1977) Television epilepsy and pattern sensitivity. *British Medical Journal*, **2**, 88–90.

WILKINS, A. J., ANDERMANN, F. and IVES, J. (1975) Stripes, complex cells and seizures. An attempt to determine the locus and nature of the trigger mechanism in pattern-sensitive epilepsy. *Brain*, **98**, 365–380.

—— DARBY, C. E. and BINNIE, C. D. Clinical aspects of pattern-sensitive epilepsy. In preparation.

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Brain (1979), **102**, 27–41

A SPINOCEREBELLAR DEGENERATION WITH X-LINKED INHERITANCE

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INTRODUCTION

THE hereditary spinocerebellar degenerations have defied adequate classification, because of the diversity of clinical features and the relative paucity of detailed neuropathological studies. The scheme of classification proposed by Greenfield (1954) remains the most satisfactory, but there are many patients with these disorders who are difficult to place in the recognized categories.

The present report describes a kindred with a spinocerebellar degeneration which is transmitted by X-linked inheritance, a rare occurrence in the hereditary ataxias. The clinical features and the mode of inheritance distinguish this condition from those reported previously.

METHODS

Electrophysiological Techniques

Motor conduction velocities were measured in the median, ulnar and lateral popliteal nerves (Table 1). Muscle action potentials were recorded with a concentric needle electrode from the abductor pollicis brevis, abductor digiti minimi and extensor digitorum brevis muscles, respectively, following supramaximal stimulation of the nerve at two sites. The conduction velocity was calculated after measuring the latency of the response from photographic records. Sensory action potentials were recorded with surface electrodes from the median and ulnar nerves at the wrist on stimulating the index and little fingers through ring electrodes (Dawson, 1956). The action potential was recorded from the lateral popliteal nerve at the neck of the fibula with subcutaneous needle electrodes on stimulating at the ankle (Gilliatt, Goodman and Willison, 1961). The sural nerve action potential was recorded with surface electrodes placed at the back of the leg and at the ankle (Burke, Skuse and Lethlean, 1974). Measurements of sural nerve conduction velocity, and the amplitude and latency to peak of sensory and mixed nerve action potentials were made on photographic records. The stimulus was a square wave of duration 0·2 ms or 0·5 ms, and of intensity up to 500 V derived from a Disa Ministim. The signals were amplified through a Tektronix FM122 preamplifier and displayed on one beam of a Tektronix 502 oscilloscope. The time scale was derived from a Devices Digitimer and was displayed on the lower beam. The temperature of the limb was measured with a thermistor and ranged from 31 to 35° C.

Histological Techniques

Sural nerve biopsy was performed on Case II-2 at the level of the lateral malleolus under local anæsthesia. A portion of the nerve was fixed in Flemming's solution, dehydrated in alcohol and embedded in paraffin wax. Transverse sections of 5 μm thickness were stained with Kulschitsky's hæmatoxylin and counterstained with Van Gieson (Gutmann and Sanders, 1943). Photomicrographs of selected fascicles were printed on photographic paper at an enlargement of × 1000. The external diameter of all myelinated fibres not undergoing active degeneration was measured to the nearest 1 μm with a rule. The area of the fascicles was measured with a planimeter and the fibre density was calculated. Another portion of the nerve was fixed in 10 per cent formalin-saline and subsequently stained for 24 hours in 1 per cent osmic acid. Single fibres were isolated by teasing (Thomas, 1955). Measurements were made of the internodal length and diameter of the individual fibres (Vizoso and Young, 1948) and the results were plotted in the manner described by Fullerton, Gilliatt, Lascelles and Morgan-Hughes (1965).

CASE REPORTS

The pedigree of the family (fig. 1) shows 64 members of whom 14 were examined by the authors, comprising 6 affected males, 2 carrier females and 6 other clinically unaffected individuals. Details of some of the other members were obtained either from hospital records or from the examined cases. There was no evidence of individuals in earlier generations having been affected, but there was an unconfirmed statement that a brother of Case I-2 suffered from the condition. Cases I-1 and I-2 were both born in South Australia and moved to New South Wales where most of their descendants now reside. Neither suffered any disturbance of gait.

Case II-1 died at the age of 71 years following a myocardial infarction. He had a history of progressive ataxia since the age of 16 years which resulted in his becoming confined to a wheelchair by the age of 30 years. He required permanent institutional care for the last twenty years of his life.

On physical examination three months before death, he was found to be a pleasant, co-operative, slow-thinking man, who was orientated in time and place. He was continent of urine and fæces. He had mild thoracic scoliosis and bilateral pes cavus. His speech was slow and scanning. Nystagmus was not present. There was cerebellar inco-ordination on finger/nose testing and on rapid repetitive movements.

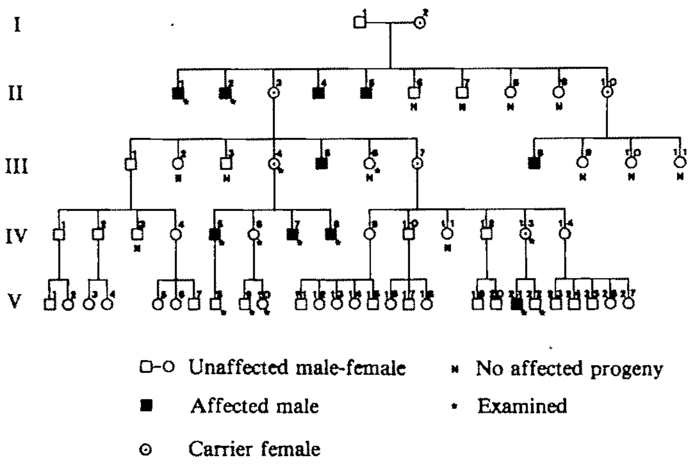

FIG. 1. Pedigree of family.

The intrinsic muscles of the hands were mildly wasted and there was marked loss of bulk in distal muscle groups of the lower limbs. Muscle tone was reduced generally and there was mild distal weakness of the upper limbs. In the lower limbs, flexor and extensor power was markedly reduced at the hips and knees and there were no voluntary movements of the ankles. Reflexes were hyperactive bilaterally with the exception of the ankle jerks which were absent. The plantar responses were extensor. Pain and temperature sense were normal, while proprioception was minimally impaired at the fingers and toes. Vibration sense was absent below the iliac crests.

Case II-2 is aged 78 years and is the only surviving affected member of this generation. At the age of 13 years he noted weakness of the lower limbs causing difficulty in running and by the age of 17 years he required crutches. At the age of 20 years he was in hospital for several years with pulmonary tuberculosis. Following discharge he was unable to walk even with crutches and he has been restricted to a wheelchair ever since. He has been in an institution for the past twenty-seven years.

Examination revealed a patient who was unable to walk but could propel himself in a wheelchair. He was orientated in time and place and gave a good history. He was continent but suffered from urgency of micturition. Bilateral pes cavus and scoliosis were present. Speech was slurred. Corrected visual acuities were R 6/9 and L 6/6. Colour vision was normal. Examination of the fundi revealed a small pigmented patch at the right macula but there was no optic atrophy. There was no nystagmus. Intention tremor, dysmetria and dysdiadochokinesia were present in the upper limbs. There was marked muscle wasting in the lower limbs and some distal wasting of the upper limb musculature. Muscle tone was minimally reduced in the arms and markedly diminished in the lower limbs. There was a mild weakness of pyramidal distribution in the upper limbs, and there was no voluntary movement of the lower limbs. All reflexes were hyperactive, with the exception of the ankle jerks which were absent. Plantar responses were extensor. Pain and temperature sensibility were normal, but there was minimal reduction in proprioception at the toes. Vibration sense was absent below the tibial tuberosities and two-point discrimination was reduced on the soles of the feet.

Cases III-4 and III-6 had no history of a neurological condition, nor abnormality on examination.

Case IV-5 is aged 35 years. He started to walk at the age of 18 months and was apparently normal until his sixth year when clumsiness of upper and lower limbs was noted which has since been gradually progressive. At the present time he is able to walk only with the help of a walking stick. His upper limb ataxia has caused great difficulty with writing since the age of 8 years. He is continent and sexual function is unimpaired. He is the only affected member of the family to have married and he has fathered a son.

On examination, he was found to be an alert and jovial male. Bilateral pes cavus, scoliosis and increased lumbar lordosis were noted. Visual acuity, colour vision and the optic fundi were normal. The gait was disturbed by a marked cerebellar ataxia and spastic diplegia. While walking he displayed truncal ataxia and titubation. Other features of cerebellar disease included a mild slurring dysarthria, nystagmus, intention tremor, dysmetria, dysdiadochokinesia and an abnormal heel-shin test. A discrepancy between the bulk of upper and lower limb musculature was noted (fig. 2). Despite wasting of some of the lower limb muscles no fasciculations were seen. Tone was normal in the upper limbs while spasticity with the clasp-knife phenomenon and ankle clonus were found in the lower extremities. There was a minimal weakness of pyramidal type in the upper limbs; in the lower limbs a moderate weakness was noted, maximal distally. Deep tendon reflexes were hyperactive, being more markedly increased in the lower limbs. Abdominal reflexes were present and plantar responses were extensor. Light touch, pain, temperature, position and vibration sense were intact and there was no Rombergism.

Case IV-6 was asymptomatic and there were no abnormalities on physical examination.

Case IV-7 (fig. 2) is now aged 30 years. He did not walk until the age of 2 years, after which development appeared normal until 15 years of age, when he first noticed difficulty in running because of clumsiness of the lower limbs. At the age of 18 years, vision in the left eye deteriorated progressively but no further change has occurred for the past eight years. His gait disturbance has gradually increased and some inco-ordination of his upper limbs has become apparent over the past ten years. There has been no incontinence nor disturbance of sexual potency.

Except for the ocular findings neurological examination was not significantly different from that in Case IV-5. Visual acuity was R 6/5 and L 6/36, and colour vision was normal. There was horizontal and vertical diplopia. The right disc was a little paler than the left but there was no optic atrophy nor degenerative retinal change. The visual disturbance was due to uniocular astigmatism.

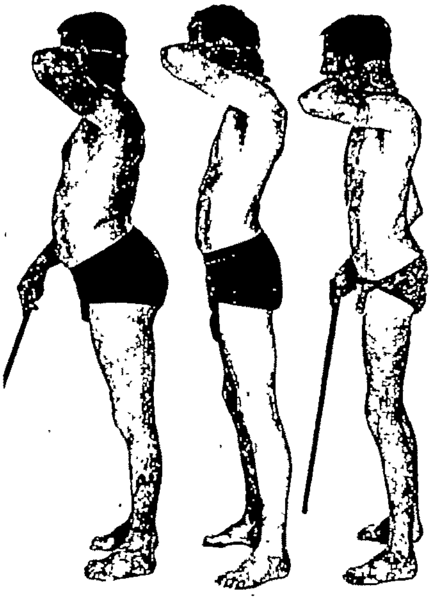

FIG. 2. Cases IV-5, IV-7 and IV-8 (left to right).

Case IV-8 (fig. 2) is aged 25 years. He first walked at the age of 18 months. Progressive clumsiness of gait and inco-ordination of upper limbs began at the age of 6 years. He has remained continent and has had no disturbance of sexual potency. Except for greater spasticity and upper motor neuron weakness in the upper limbs, the physical findings were similar to those of Case IV-5.

Case IV-13 was asymptomatic and normal on physical examination.

Case V-8 is aged 8 months and was born at term following a normal pregnancy and labour. His development has so far been normal and no abnormality was found on physical examination.

Cases V-9 and V-10 were normal.

Case V-21 now aged 5 years, was first seen at the age of 3 years. His gait was unsteady and there was nystagmus and inco-ordination of the upper limbs. Tone was increased in the lower limbs and knee and ankle jerks were exaggerated. Plantar responses were flexor.

He was reviewed two years later when his ataxia had increased and there were bilateral extensor plantar responses.

Case V-22 was aged 11 months when first seen and was found to be normal. He was reviewed two years later and it was noted that he had commenced walking at 12 months. He had normal dexterity and the physical examination remained unremarkable.

RESULTS

Summary of Clinical Findings

The first expression of this condition is the late onset of walking (18 months to 2 years of age). In the first or second decade, gradually progressive ataxia of gait and inco-ordination of the upper and lower limbs became evident and by the early twenties walking sticks may be required. The two older members (Cases II-1 and II-2 were confined to a wheelchair by the age of 30 years and required permanent hospital care by the time they were 50 years old.

Incontinence, dementia, and impairment of vision are not features of this condition. Life expectancy does not seem to be affected.

On examination, pes cavus, scoliosis and increased lumbar lordosis are present. There are signs of marked cerebellar dysfunction, characterized by slurring dysarthria, intention tremor and dysmetria. Nystagmus is a variable feature being mild in the younger members and absent in the two older cases (II-1 and II-2). There is a very slowly progressive wasting of muscles of the lower limbs and minimal wasting distally in the upper limbs. In the younger cases spasticity was observed, but hypotonia was present later in the disease. Weakness of pyramidal type was present, with hyperactive deep tendon reflexes and extensor plantar responses. Sensory abnormalities were noted on clinical examination only in the two older patients, and consisted of impairment of position and vibration sense.

Electrocardiography

No abnormalities were noted in the electrocardiograms obtained from Cases IV-5, IV-7, IV-8 nor IV-21. In Cases II-1 and II-2 mild ischæmic changes were found.

Electrophysiological Studies

The results of nerve conduction studies are summarized in Table 1.

The control values for the median, ulnar and lateral popliteal nerves were obtained from 35 normal subjects matched for age (McLeod, Walsh, Prineas and Pollard, 1976). The control figures for the sural nerve conduction velocity were from 79 normal subjects aged 8 to 74 years (Burke, Skuse and Lethlean, 1974).

TABLE 1. NERVE CONDUCTION STUDIES

	Motor conduction					*Sensory conduction*						*Mixed nerve action potential*
	Median		*Ulnar*		*Lateral popliteal*	*Median*		*Ulnar*		*Sural*		*Lateral popliteal*
	Latency	*MCV*	*Latency*	*MCV*	*MCV*	*Latency*	*Amplitude*	*Latency*	*Amplitude*	*Amplitude*	*CV*	*Amplitude*
Patient	*ms*	*m/s*	*ms*	*m/s*	*m/s*	*ms*	*μv*	*ms*	*μv*	*μv*	*m/s*	*μv*
II-1	5·4	45	3·0	41	NR	4·5	3	NR	NR	—	—	NR
II-2	4·9	35	3·0	40	NR	4·7	6	3·9	3	—	—	NR
IV-5	4·7	34	3·3	39	36	4·7	6	3·3	7	4	38	1
IV-7	4·9	41	3·0	44	38	3·3	8	3·5	5	8	33	1
IV-8	5·1	39	3·6	40	40	3·1	10	3·4	10	5	33	2
V-21	3·2	39	2·0	46	—	2·6	20	—	—	—	—	—
Control mean	3·4	56·9	2·6	55·7	47·3	3·0	17·9	2·5	13·7	16·4	46·2	6·7
SD	0·5	5·0	0·4	4·6	4·9	0·3	7·5	0·3	6·4	5·5	3·7	3·7

NR = Not recordable. — = Not tested. SD = Standard deviation of mean.

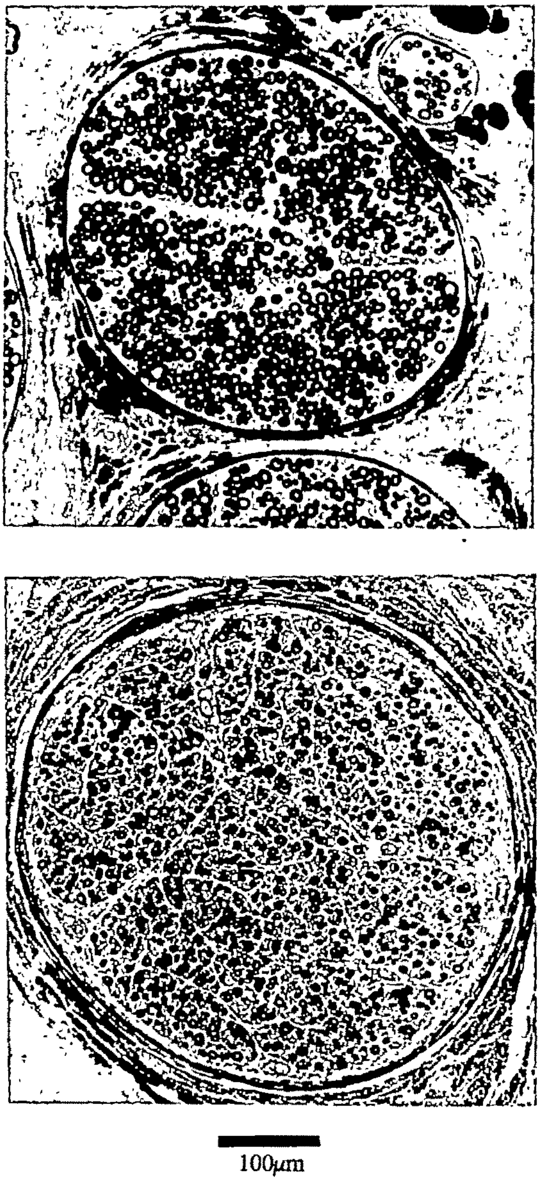

FIG. 3. Transverse sections of fascicles from sural nerve of control (*above*) and Case II-2 (*below*). Flemming, Kultchitsky, van Gieson.

Motor conduction velocities were reduced in all the nerves tested and no motor response was obtained in the extensor digitorum brevis muscle on stimulating the lateral popliteal nerves in the 2 older members (II–1 and II–2).

Sensory action potentials were obtained from all nerves tested except the ulnar nerve of Case II–1. However, in all but the younger affected members (IV–8 and V–21) there was reduction in the amplitude and increased latency. The abnormalities were most marked in the older affected members.

The conduction velocities in the sural nerves were reduced.

Sural Nerve Biopsy

In the sural nerve biopsy obtained from II–2, no onion-bulb formations were seen and the fibres appeared normally myelinated. The density of myelinated fibres was 4752 fibres/sq mm, which is within the control range of 3819–6420 fibres/sq mm (Walsh, 1971). It may be seen however, from figs. 3 and 4 that there is a marked reduction in the density of the large diameter fibres. The density of fibres greater than 8 μm in diameter was 302/sq mm which is well below the control range of 1284–1993/sq mm (Walsh, 1971).

Most of the teased fibres appeared to be normally myelinated and no fibres were seen to be undergoing active degeneration. It may be seen from fig. 5 that there was little variability in the internodal lengths of individual fibres and that the internodal lengths tended to be short.

Autopsy Findings

At post-mortem examination of Case II–1 (82 hours after death) it was found that he had died of a large myocardial infarction. The coronary arteries were slightly atheromatous. There was an extensive region of infarction, of at least some weeks to months duration, in the posterior wall of the left ventricle. The remainder of the heart was macroscopically normal but insufficient material was available for adequate microscopic examination.

The brain weight was 1090 g and there was evidence of a slight diffuse cerebral atrophy. Macroscopically the cerebellum was small. Blocks were taken from several levels of the spinal cord, medulla, pons, midbrain, cerebellum, striatum and cerebral cortex. They were embedded in paraffin wax and stained with hæmatoxylin and eosin, and luxol fast blue/cresyl violet. Selected sections were stained with phosphotungstic acid hæmatoxylin and by the Weigert-Pal method.

In the cerebellum there was extensive loss of Purkinje cells. The Bergmann glia were prominent and there was loss of cells from the granular layer (fig. 6). These changes were seen in both the vermis and hemispheres but were most marked on the dorsal surface. The neurons of the dentate nucleus were a little reduced in number and many astrocytes were seen both within and immediately surrounding the nucleus. There was loss of neurons and myelin with accompanying gliosis in the medial portion of the upper one-third of the dorsal leaf of the inferior olive (fig. 7). There was some loss of myelin from the inferior cerebellar peduncles. No

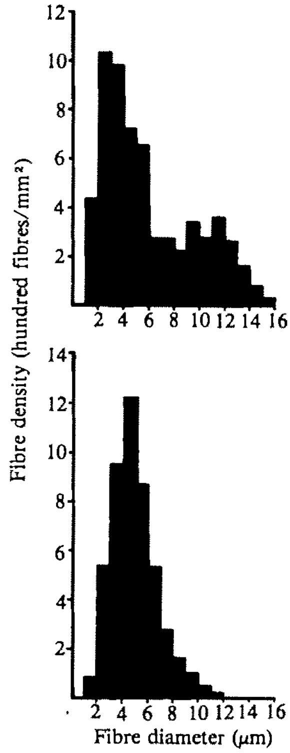

FIG. 4. Distribution of diameters of myelinated fibres in sural nerves of control (*above*) and Case II-2 (*below*).

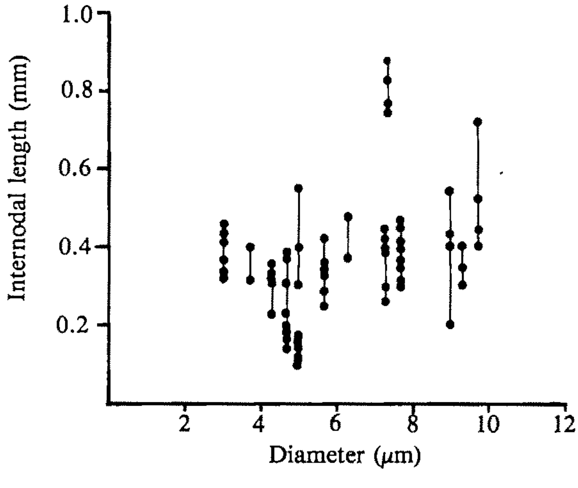

FIG. 5. Distribution of internodal lengths in single fibres teased from sural nerve of Case II-2. Lengths of internodes in individual fibres are plotted against diameter of widest internode and joined by a vertical line.

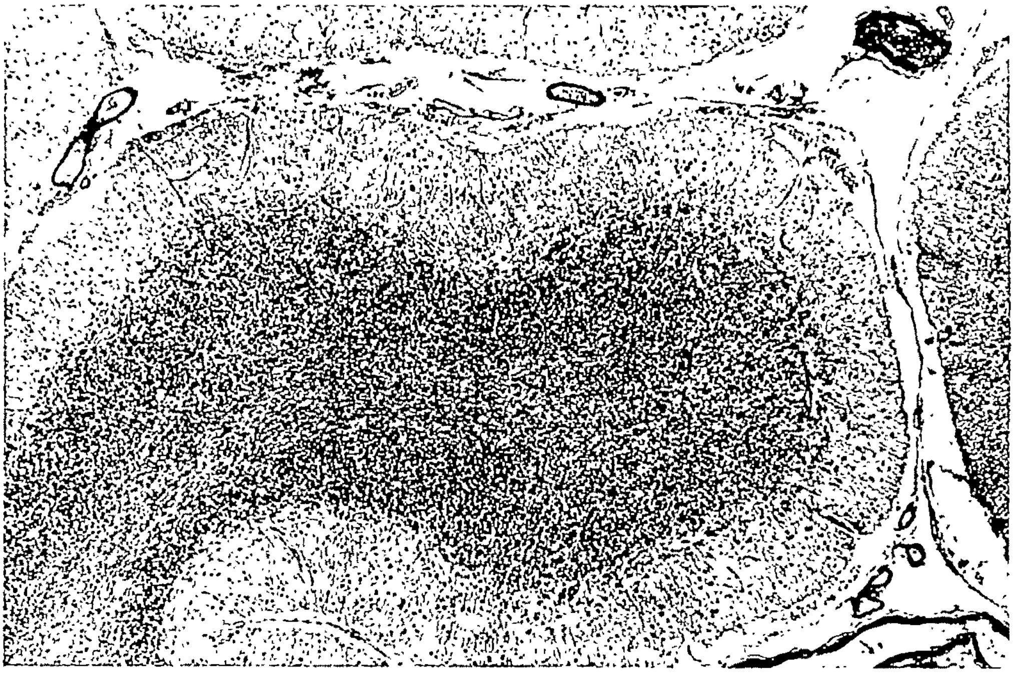

FIG. 6. Case II-1. Folia of cerebellum. There is a pronounced loss of Purkinje cells. Hæmatoxylin and eosin. ×40.

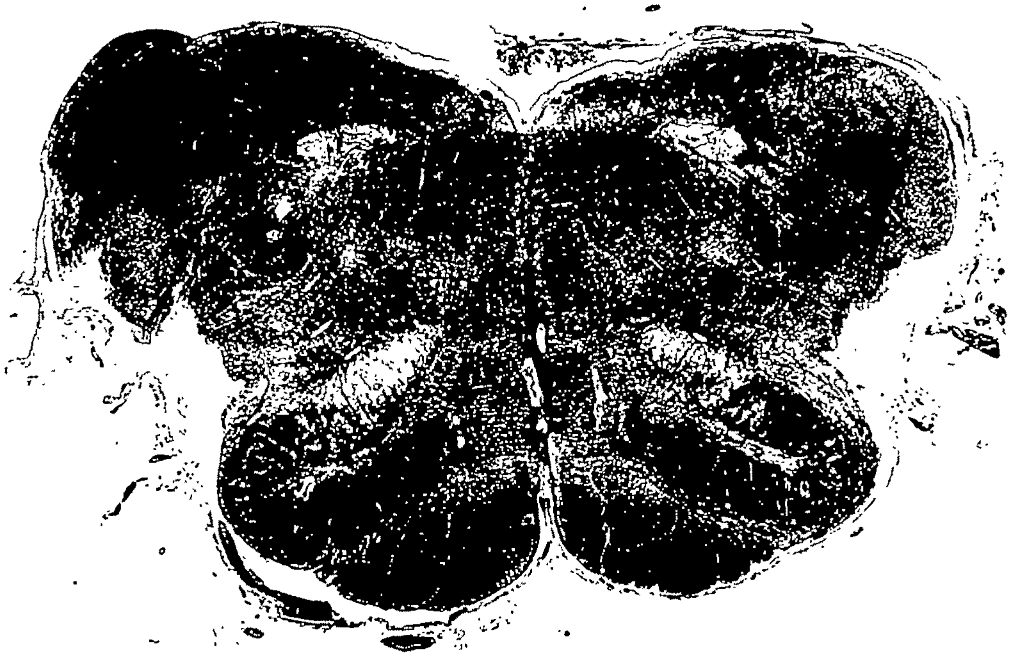

FIG. 7. Case II-1. Medulla. There is a loss of myelin and cells in medial portion of dorsal leaf of inferior olive. Luxol-fast blue. ×7.

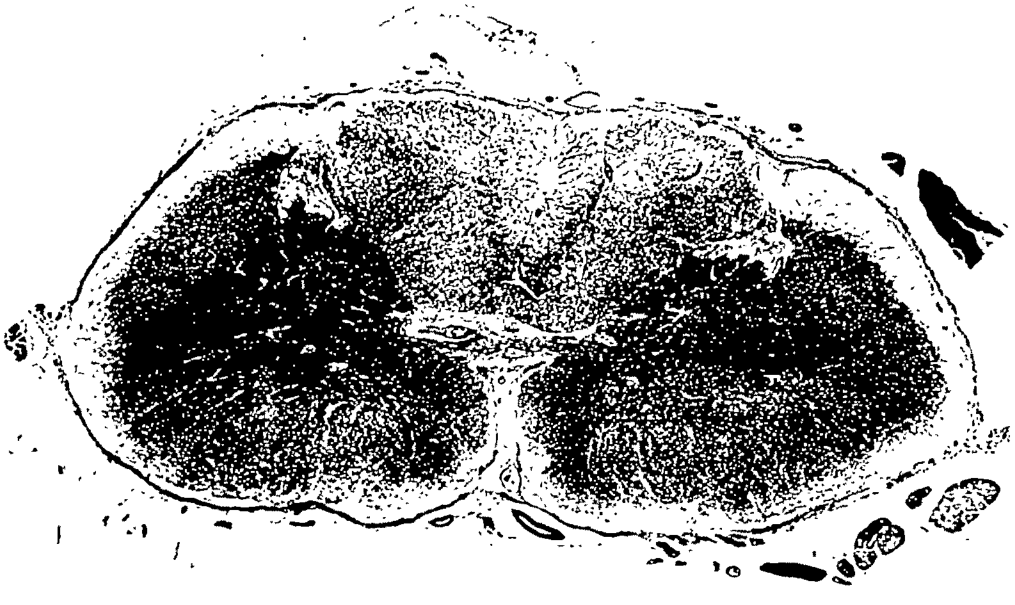

FIG. 8. Case II-1. Cervical cord. There is partial loss of myelin from the dorsal columns and spinocerebellar tracts. There has been some separation of pia from the cord. Luxol-fast blue. ×11.

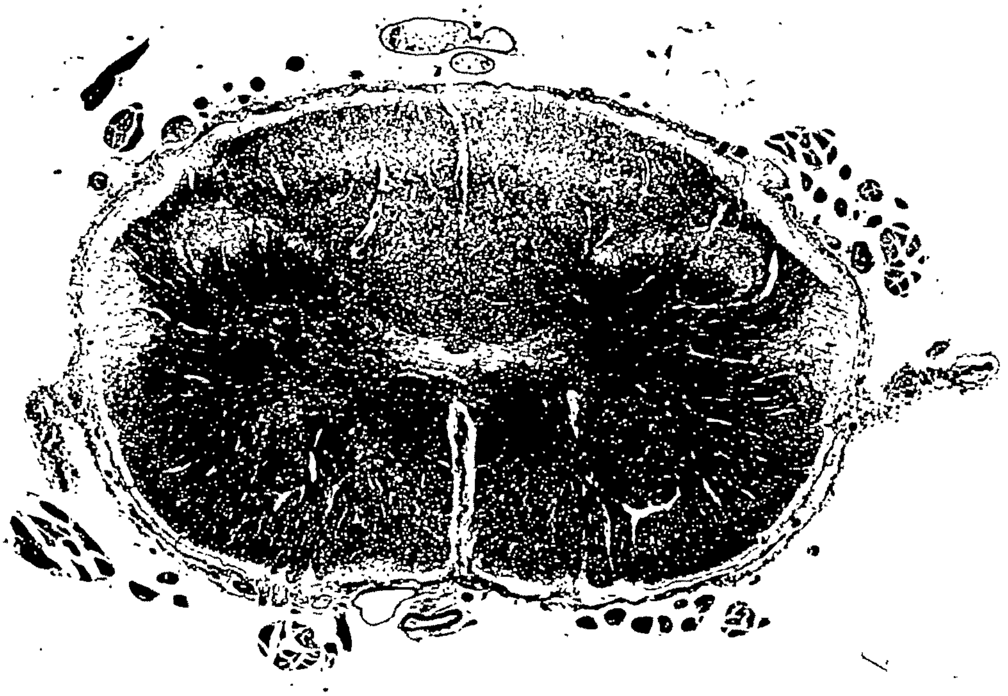

FIG. 9. Case II-1. Lumbar cord. There is partial loss of myelin from the dorsal columns and corticospinal tracts. There has been some separation of the pia from the cord. Luxol-fast blue. ×11.

abnormality was seen in either the longitudinal or transverse fibres of the pons or middle cerebellar peduncles. There was some pallor of the superior cerebellar peduncles. In the cervical cord there was partial loss of myelin from the spinocerebellar tracts and posterior columns, the changes in the latter being more marked in the fasciculus gracilis (fig. 8). In the lumbar cord there was extensive loss of myelin from the posterior columns and from the region occupied by the corticospinal tracts (fig. 9). There were some artefactual changes in the periphery of the spinal cord sections due to post-mortem autolysis.

DISCUSSION

Although the disorder seen in this kindred has some features in common with Friedreich's ataxia, it differs in several respects. The long survival of the affected members is unusual for Friedreich's ataxia, in which Bell and Carmichael (1939) found the average age at death to be 26·5 years in those cases with autosomal recessive inheritance. Andermann, Remillard, Goyer, Blitzer, Andermann and Barbeau (1976), in a detailed analysis of 35 sibships in which 58 individuals were affected by Friedreich's ataxia, found that autosomal recessive inheritance was almost invariable; the average age of death in their series was 30·6 years. Of the 10 affected members in the present kindred, 3 died after the age of 60 years and, of the 7 surviving patients, 3 are above that age. Moreover, the exaggerated tendon reflexes, the amyotrophy and the relatively minor sensory changes are all features which are atypical of Friedreich's ataxia.

In the pedigree (fig. 1), there are 10 affected members, all males, and the condition is transmitted through clinically unaffected females in a manner typical of X-linked recessive inheritance. However, the possibility of dominant inheritance with sex limitation cannot be excluded as Case IV-5 is the only affected member to have married and fathered a child and his son is below the age at which the condition is first manifested. The spinocerebellar degenerations most commonly display autosomal recessive inheritance and show little variability in expression between the sexes (Bell and Carmichael, 1939; Sjögren, 1943; Hariga and Moutschen, 1969); but a sex-limited form of the Roussy-Levy syndrome has been reported (Popow, 1932). Examples of X-linked inheritance are rare, and the clinical features vary in the families with Friedreich's ataxia in which only males were affected with transmission through clinically unaffected females. In the kindred described by van Bogaert and Moreau (1939), features of Friedreich's ataxia were associated with those of peroneal muscular atrophy, the disorder being transmitted by clear X-linked recessive inheritance. Another type of spinocerebellar degeneration with this form of heredity was described by Malamud and Cohen (1958). The affected members of that family had a rapidly progressive disorder in which cerebellar ataxia was associated with extrapyramidal signs. Shokeir (1970) described three families with X-linked recessive inheritance of a cerebellar ataxia. Onset was between 16 and 21 years of age, and the course was progressive until the age of 30 years, after which no further deterioration occurred. Pyramidal tract signs were minimal and there were no sensory abnormalities. The condition in the present family has features which differentiate it from these other X-linked recessive ataxias and represents another clinical type of spinocerebellar syndrome determined by mutations on the X chromosome.

The pathological findings of degeneration of the dorsal columns, spinocerebellar tracts, and to a lesser extent, the corticospinal tracts in the spinal cord are similar to those in Friedreich's ataxia although the marked loss of Purkinje cells in the cerebellum is greater than that usually seen in that condition. The loss of large diameter fibres in the sural nerve, and the finding of uniformly short internodal lengths are also features of Friedreich's ataxia (Dyck and Lambert, 1968; McLeod, 1971).

Despite these similarities in peripheral nerve pathology, the electrophysiological findings contrast with those seen in Friedreich's ataxia in which there are usually normal or only mildly slowed motor conduction velocities and sensory action potentials which are absent or only rarely recordable (Hughes, Brownell and Hewer, 1968; McLeod, 1971; Oh and Halsey, 1973; Salisachs, Codina and Pradas, 1975). In the present kindred, on the other hand, all motor conduction velocities were below the normal range while sensory action potentials, although reduced in amplitude, were obtained from all but one of the nerves tested in the six affected members. The electrophysiological findings correlate with the more marked amyotrophy and less obvious sensory impairment in the present kindred than that usually found in Friedreich's ataxia.

SUMMARY

A spinocerebellar degeneration is described affecting ten members of a family over five generations with transmission by X-linked recessive inheritance.

The clinical features include pes cavus, scoliosis, increased lumbar lordosis and signs of cerebellar dysfunction. There is a slowly progressive distal muscle atrophy, pyramidal weakness, brisk tendon jerks and the plantar responses are extensor. Sensory abnormalities were observed only in the two eldest members and consisted of mild impairment of position and vibration sense.

A sural nerve biopsy showed loss of large diameter fibres and uniformly short internodal lengths as is usually found in Friedreich's ataxia. However, the electrophysiological findings of retained sensory action potentials and reduced motor conduction velocities contrast with those of Friedreich's ataxia.

Post-mortem examination of one of the affected members revealed spinal cord pathology similar to that seen in Friedreich's ataxia with degeneration of the dorsal columns, and spinocerebellar and corticospinal tracts although the loss of Purkinje cells in the cerebellum was greater than is usually seen in that condition.

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REFERENCES

ANDERMANN, E., REMILLARD, G. M., GOYER, C., BLITZER, L., ANDERMANN, F. and BARBEAU, A. (1976) Genetic and family studies in Friedreich's ataxia. *Canadian Journal of Neurological Sciences*, **3**, 287–301.

BELL, J. and CARMICHAEL, E. A. (1939) On hereditary ataxia and spastic paraplegia. In: *Treasury of Human Inheritance*. London: Cambridge University Press, Vol. IV, pp. 141–281.

BURKE, D., SKUSE, N. F. and LETHLEAN, A. K. (1974) Sensory conduction of the sural nerve in polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 647–652.

DAWSON, G. D. (1956) The relative excitability and conduction velocity of sensory and motor nerve fibres in man. *Journal of Physiology, London*, **131**, 436–451.

DYCK, P. J. and LAMBERT, E. H. (1968) Lower motor and primary sensory neuron disease with peroneal muscular atrophy. II. Neurologic, genetic and electrophysiological findings in various neuronal degenerations. *Archives of Neurology, Chicago*, **18**, 619–625.

FULLERTON, P. M., GILLIATT, R. W., LASCELLES, R. G. and MORGAN-HUGHES, J. A. (1965) The relation between fibre diameter and internodal length in chronic neuropathy. *Journal of Physiology, London*, **178**, 26–28.

GILLIATT, R. W., GOODMAN, H. V. and WILLISON, R. G. (1961) The recording of lateral popliteal nerve action potentials in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **24**, 305–318.

GREENFIELD, J. G. (1954) *The Spinocerebellar Degenerations*. Springfield, Illinois: Charles C. Thomas.

GUTMANN, E. and SANDERS, F. K. (1943) Recovery of fibre numbers and diameters in the regeneration of peripheral nerves. *Journal of Physiology, London*, **101**, 489–518.

HARIGA, J. and MOUTSCHEN, J. (1969) On the inheritance of heredoataxias. *Human Heredity*, **19**, 457–472.

HUGHES, J. T., BROWNELL, B. and HEWER, R. L. (1968) The peripheral sensory pathway in Friedreich's ataxia. *Brain*, **91**, 803–818.

MCLEOD, J. G. (1971) An electrophysiological and pathological study of peripheral nerves in Friedreich's ataxia. *Journal of the Neurological Sciences*, **12**, 333–349.

—— WALSH, J. C., PRINEAS, J. W. and POLLARD, J. D. (1976) Acute idiopathic polyneuritis. A clinical and electrophysiological follow-up study. *Journal of the Neurological Sciences*, **27**, 145–162.

MALAMUD, N. and COHEN, P. (1958) Unusual form of cerebellar ataxia with sex-linked inheritance. *Neurology, Minneapolis*, **8**, 261–266.

OH, S. Y. and HALSEY, J. M. (1973) Abnormality in nerve potentials in Friedreich's ataxia. *Neurology, Minneapolis*, **23**, 52–54.

POPOW, A. (1932) Une famille atteinte d'une forme particulière de maladie héréditaire (Forme de Roussy-Lévy). *Revue Neurologique*, **2**, 447–462.

SALISACHS, P., CODINA, M. and PRADAS, J. (1975) Motor conduction velocity in patients with Friedreich's ataxia. Report of 12 cases. *Journal of the Neurological Sciences*, **24**, 331–337.

SHOKEIR, M. H. K. (1970) X-linked cerebellar ataxia. *Clinical Genetics*, **1**, 225–231.

SJÖGREN, T. (1943) Klinische und erbbiologische untersuchungen uber die heredoataxien. *Acta Psychiatrica, Copenhagen*. Supplement 27, 1–197.

THOMAS, P. K. (1955) Growth changes in the myelin sheath of peripheral nerve fibres in fishes. *Proceedings of the Royal Society B*. **143**, 380–391.

TURNER, E. V. and ROBERTS, E. (1938) A family with sex-linked hereditary ataxia. *Journal of Nervous and Mental Diseases*, **87**, 74–80.

VAN BOGAERT, L. and MOREAU, M. (1939) Combinaison de l'amyotrophie de Charcot-Marie-Tooth et de la maladie de Friedreich chez plusieurs membres d'une même famille. *Encéphale*, **34**, 312–320.

VIZOSO, A. D. and YOUNG, J. Z. (1948) Internode length and fibre diameter in developing and regenerating nerves. *Journal of Anatomy, London*, **82**, 110–134.

WALSH, J. C. (1971) The neuropathy of multiple myeloma. An electrophysiological and histological study. *Archives of Neurology, Chicago*, **25**, 404–414.

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Brain (1979), **102,** 43–63.

SEMANTIC ACCESS DYSLEXIA

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INTRODUCTION

BOTH neurologists and psychologists have adopted a topographical approach to the problem of acquired dyslexia. Neurologists have been primarily concerned with the distinction between dyslexia with dysgraphia, and dyslexia without dysgraphia; the classical interpretations of such syndromes have contrasted 'disconnection' lesions and 'centre' lesions. Psychologists, on the other hand, being more concerned with identifying and specifying the systems involved in reading, have postulated different 'routes' to word meaning.

The existence of patients not able to read or understand the written word but able to write words and sentences, both spontaneously and to dictation, led to the inference that a hypothetical centre must be intact but disconnected from incoming information. Furthermore in those patients who are not only unable to read but are also unable to write it was generally held that the central representation of written letters and words itself was damaged. This formulation of dyslexic syndromes has been much strengthened by the accumulating evidence on the anatomical basis of these syndromes. In spite of drawing upon a source, intrinsically variable and not subject to experimental control, the individual patient in whom post-mortem data were available, there is remarkable agreement as to the critical anatomical structures implicated. A lesion in the region of the angular gyrus together with, in the majority of patients, involvement of the splenium, is associated with dyslexia without dysgraphia, and a lesion in the region of the supramarginal gyrus with dyslexia with dysgraphia (cf. Benson and Geschwind, 1969).

On a different level of analysis the approach of experimental psychologists has been somewhat analogous. In the early 1970s reading skills were investigated within the framework of information-processing models. Analysis in terms of the organization of stages and the transmission of information between stages focuses on the respective contribution of transmission through a phonological system and transmission directly from the visual word-form to the semantic system ('direct route'). (Following Rommetveit (1968) we use the former term to refer to the written word as a visual Gestalt or pattern. In earlier papers we misleadingly referred to it as a 'grapheme'.) Neuropsychological data have reinforced the validity of this approach with the identification of different types of acquired dyslexia thought to arise from damage to one or other of these routes, phonemic (deep) dyslexia and semantic (surface) dyslexia, respectively (cf. Marshall and Newcombe, 1973).

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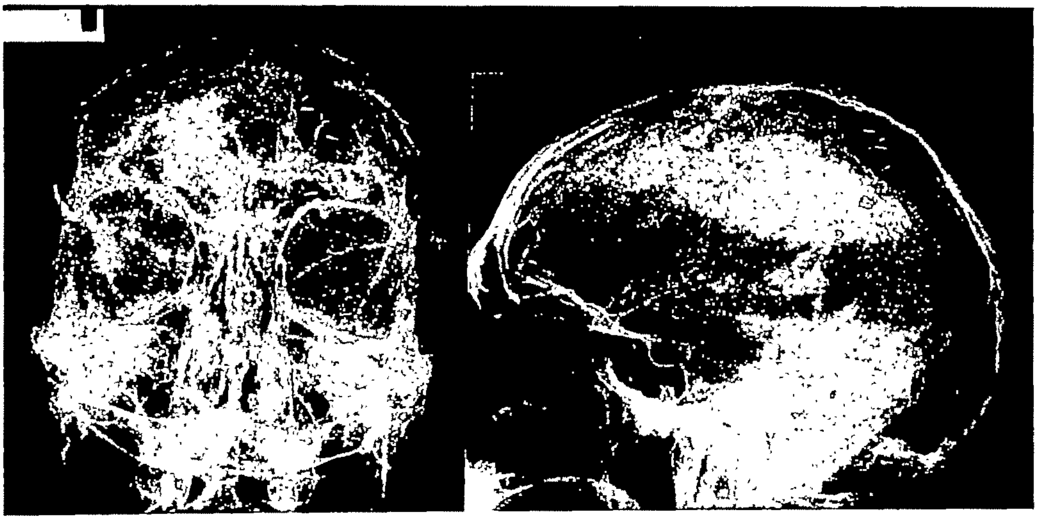
However, few neurologists or psychologists, at least in the area of reading disorders, have attempted the analysis of the properties of any of the sub-systems involved. Saffran and Marin (1977) provide one notable exception by investigating the properties of the visual word-form in a phonemic dyslexic patient, who was restricted to reading by the 'direct route'. At a more theoretical level, in their original speculations regarding deep dyslexia, Marshall and Newcombe (1966) used Katz and Fodor's (1964) theory and attributed certain aspects of reading impairment to a failure of the patient to encode the lower hierarchical levels of the lexical entry in the specification of the appropriate phonological form.

Recent investigations of patients with visual object agnosia suggest that an analytical approach to dyslexia might provide some insight into the nature of the mechanisms of recognition achieved by the direct route in patients unable to resort to using the phonological route. Visual object agnosia (associative agnosia), the failure to identify objects by naming or functional description, in spite of adequate processing at a sensory or perceptual level, has also been treated traditionally by neurologists within the framework of 'disconnections' and centres. However, the investigation of semantic categorization skills in patients with visual object agnosia has brought to light some interesting phenomena (Taylor and Warrington, 1971; Hécaen, Goldblum, Masure and Ramier, 1974; Warrington, 1975; Schwartz, Marin and Saffran, 1979). More specifically it would appear that these patients are able to access some levels of semantic information on occasions where there was insufficient semantic information accessed for precise identification: for example a *canary* can be known to be a bird but not that it is yellow. Warrington (1975) has claimed that there is an invariant order of dissolution of semantic knowledge, low frequency items being more vulnerable than high frequency items, and subordinate category information being more vulnerable than superordinate information. An analogous observation may have been recorded in a dyslexic patient. Albert, Yamadori, Gardner and Howes (1973) described a patient JH in whom there was a dissociation between reading aloud, which was very impaired, and the capacity to understand the meaning of written words. In particular the authors suggest that his residual abilities could be characterized as the comprehension of word meanings within broad semantic spheres.

In this study we report our investigations of a patient having dyslexia without dysgraphia. As the 'phonological' route was inoperative he provided an opportunity to investigate the properties of the 'direct' route recognition mechanism. In particular we have examined his capacities on categorization tasks and phenomena which would suggest partial or incomplete access to the semantic representation of the written word.

CASE REPORT

AR, a 60-year-old right-handed printer, was admitted to the National Hospital under the care of Mr. Lindsay Symon in November, 1971. Left carotid angiography showed a 1·5 cm midline shift towards the right and a large avascular mass in the left parietal lobe. A burr hole biopsy was performed and a left parietal intracerebral abscess was confirmed and aspirated. The residual lesion was visualized by Stereopaque (*see* fig. 1). AR made a slow recovery and two months later he was discharged to a convalescent home. At this time, he was still severely aphasic and agnosic, so that formal psychometry could not be attempted. There was a mild right hemiparesis and a complete right hemianopia which have persisted unchanged.



One year later, in March, 1972, he was referred to the Psychology Department for investigation of his incapacitating reading difficulty which was static and not improving, unlike his other cognitive functions. He was seen at irregular intervals in the Psychology Department over the next four years during which time there appeared to be no change in his cognitive skills and in particular, his dysphasia and dyslexia neither improved nor worsened. He was tested on the WAIS in January, 1975, and obtained a verbal IQ of 107 and a performance IQ of 101. He was also tested on the Progressive Matrices and scored 35/60, equivalent to an IQ of 114 corrected for age. The detailed account of his cognitive functions which follows is collated from test data obtained during the period March 1972 to July 1976.

His language functions apart from a very marked nominal dysphasia were relatively well-preserved. He was tested on the Coughlan/Warrington (1978) tests of word retrieval; his object-naming was very poor (scoring only 1/15). In contrast he had little difficulty in naming objects from their description (for example, what is the name of the grey animal with a trunk?) scoring 11/15. This pattern of disability in the neurological literature is termed 'optic aphasia' (Freund, 1889; Lhermitte and Beauvois, 1973). Informal observation suggested that there was no sparing for any class of object name and that he had equal difficulty with animate and inanimate objects, colours and parts of the body. His spoken speech was somewhat halting but for the most part accurate with regard to word choice and syntax. There was no evidence of visual object agnosia; for instance, he had no difficulty in describing objects by their function. On a test probing knowledge of visual objects (pictures) he scored 49/60, which is only just below the normal range, and on a test probing knowledge of pictures of animals he scored 56/60, which is within the normal range (Warrington, 1975).

AR's reading skills were investigated in more detail at a clinical level. He was unable to read individual letters with any degree of accuracy, his score in reading letters ranging from 10/26 to 20/26 on different occasions. His difficulty went beyond a mere naming deficit in so far as he made errors in matching upper and lower case letters (16/20). Further, in a test requiring him to point to the odd letter in a series of three mixed upper and lower case letters (for example, f F e) he scored 4/10. On these tests of letter identification he generally appeared to be unaware whether or not he had responded correctly or whether or not he had succeeded in correctly naming a letter. Though he could repeat the alphabet aloud correctly he could not arrange wooden letters in their correct alphabetical order. His letter-naming by touch was also impaired; he named 7/26 letters with the right hand and 12/26 letters with his left hand. In contrast he had little difficulty in naming (48/50) or pointing to named numbers (41/50). AR was asked to categorize individual letters as belonging to the beginning, middle or end of the alphabet. He could do this fairly accurately and scored 58/78 (a chance score being 26/78).

AR was presented with 36 pairs of letters separated by 5 letters and 28 pairs of letters separated by 9 letters (all possible combinations excluding A and Z were used twice). He was first asked to say which letter came first in the alphabet, he was then immediately asked to name each of the pair. He scored 75 per cent and 86 per cent respectively on the categorization task. This level of performance is significantly above that expected by his naming ability: considering only those trials on which he failed to name either letter his categorization score was 16/22 correct ($\chi^2 = 4{\cdot}55$, $P < 0{\cdot}05$).

His ability to read individual words was also gravely impaired; on the Schonell graded reading test he scored 18/100 (12/100 on a separate occasion) and on the Nelson test he scored 2/50. In contrast, he scored 66/100 on the Schonell graded spelling test (writing each word to dictation) which is only mildly impaired, the normal range being between 80 and 100. His oral spelling was somewhat better, he scored 32/40 on 2 of the 5 sets of graded words from the Schonell list. He thus can be accepted as a patient with dyslexia without dysgraphia.

AR's ability to read three-letter words printed singly on cards presented across the desk was compared with his ability to read the same three-letter words presented tachistoscopically for 100 ms. An ABBA-BAAB design was used and AR attempted 15 words in each block. He read 17/60 words presented tachistoscopically and 24/60 words presented for unlimited time across the desk. This difference in level of performance was not significant.

AR was asked to read two sets of three-letter nonsense syllables on two separate occasions and he succeeded in reading 5/20 and 7/25 respectively. The correct responses occurred on those occasions when he succeeded in sounding or naming correctly all three letters of the nonsense syllable.

In summary, AR was a patient able to function between the average and high average levels on tests of intelligence. There was a marked nominal dysphasia, other aspects of language comprehension and expression being relatively well preserved. He was able to write and spell fairly satisfactorily but he had a grave impairment in his ability to read written letters and words. This syndrome, dyslexia without dysgraphia, is the subject of the following experimental investigation.

EXPERIMENTAL INVESTIGATION

More detailed investigations of AR's reading difficulties may be divided into three sections. We first obtained a corpus of his responses when reading individual words. Then we have attempted to show that difficulties in the naming process, as contrasted with the comprehension process, could not account for his reading problems. Finally we have examined in more detail the particular characteristics of his difficulty in comprehension of written words.

Reading Level

AR attempted to read the following sets of words in test sessions spread over a three-year period:

(1) *AA* words with less than 8 letters from the Thorndike-Lorge (1944) list. 968 words were presented individually on index cards and 48 per cent were read correctly.

(2) *AA* words from the Brown and Ure (1969) list. 199 words were presented individually and 49 per cent were read correctly;

(3) *A* words from the Brown and Ure list. 85 words were attempted and he read 42 per cent correctly;

(4) low frequency words (1—50) from the Brown and Ure list. 339 words were attempted; he read 37 per cent correctly;

(5) *AA* and *A* words from the Paivio, Yuille and Madigan (1968) list. This set of words was attempted on two separate occasions in order to obtain a consistency measure. He read 22 per cent and 37 per cent correctly, respectively. (Towards the end of his attempt on the first occasion to read these words AR was clearly very fatigued and failed to read 43 words consecutively).

Overall there were 42·5 per cent correct responses, 36·8 per cent omissions, 19·2 per cent errors and 1·3 per cent responses which consisted of letters. Five aspects of his word-reading performance will be considered: the effects of syntactic class, imageability/concreteness and word length on the probability of a correct response, the consistency of his responses and the pattern of his errors.

(1) AR's ability to read 780 of the *AA* words that were judged relatively unambiguous in syntactic class (function words were arbitrarily assigned to what was judged the most appropriate syntactic class) was analysed. There was no major effect of syntactic class: Nouns (312 words) 54 per cent correct; Adjectives (138 words) 63 per cent correct; Verbs (191 words) 37 per cent correct; Adverbs (42 words) 52 per cent correct; Pronouns (34 words) 68 per cent correct, and Prepositions/Conjunctions (63 words) 40 per cent correct. This pattern differs strikingly from that observed in all phonemic/deep dyslexic patients on whom comparable data have been reported (Marshall and Newcombe, 1966; Shallice and Warrington, 1975; Patterson and Marcel, 1977; Saffran and Marin, 1977). For example, in AR the reading of function words was no more impaired than content words.

(2) The effect of imageability/concreteness varied from negligible (on the Brown and Ure AA words) to considerable (on the Paivio AA words (*see* Table 1)). There appeared to be a complex interaction between this effect and part of speech, the effect of imageability being primarily restricted to nouns (the Paivio list contains only nouns). The imageability/concreteness effect was, however, much weaker than

TABLE 1. PERCENTAGE OF HIGH AND LOW CONCRETENESS (C)/IMAGEABILITY (I) WORDS READ FROM FIVE WORD POOLS

	C/I	*No. of words*	*% Correct*	
			High	*Low*
Brown and Ure AA	C	199	53	45
Brown and Ure A	C	85	47	40
Brown and Ure 1-50	C	278	53	30
Paivio, *et al.* HF 1	I	270	28	10
Paivio, *et al.* HF 2	I	270	44	24

for KF (Shallice and Warrington, 1975), who read correctly only 3 per cent of the Brown and Ure 1—50 low concrete words, in contrast with AR's 30 per cent.

(3) There was only a slight effect of word length when investigated on the Brown and Ure 1—50 high concrete, low frequency pool (mean length of words correct = 5·37, mean length of words failed = 5·91).

(4) AR's performance on the set of words attempted on two occasions (Paivio *et al.*, Nouns) was very inconsistent. Dividing his responses simply into correct and incorrect there was a contingency coefficient of only 0·31 between the two sets of responses. If this value is recomputed ignoring the last 50 responses (when his level of response was very poor) the value of C (0·34) is virtually unchanged. By comparison on the identical words KF had a contingency coefficient of 0·56 (maximum = 0·71). However, other patients with phonemic dyslexia have been reported to give inconsistent responses (Marshall and Newcombe, 1966; Saffran and Marin, 1977).

(5) AR's 409 errors were subdivided according to the classification used with KF (Shallice and Warrington, 1975):

Visual (e.g. *tired—timed*), 57 per cent.
Derivational semantic (e.g. *necessity—necessary*), 6 per cent.
Non-derivational semantic (e.g. *month—week*), 5 per cent.
Semantic/visual (e.g. *paper—page*), 12 per cent.
Others, 20 per cent.

The large size of the 'other' categories is due to AR's making many responses which had only the initial letters in common with the stimulus and so failing the rather strict 'visual' criterion, for example, plant—plus, famous—father; none of these responses were neologisms. Very varied error patterns have been reported in phonemic dyslexics; the major difference noted in AR is the low rate of semantic derivational errors.

Word Comprehension and Nominal Dysphasia

The data reported in the previous section establish that AR's ability to read words aloud was gravely impaired. AR had a very marked nominal dysphasia which had all the hallmarks of an 'optic aphasia' (*see* Case Report above). It was therefore all the more necessary to consider the possible contribution of a naming deficit to his reading abilities. A series of tests were devised to establish that his word recognition difficulties could not be accounted for by his severe nominal dysphasia.

Experiment 1. The Peabody Picture Vocabulary Test. The PPVT (Form A) was administered according to the standard procedure. This requires a spoken word/picture match. For comparison the PPVT (Form B) was adapted by requiring AR to match the written word instead of the spoken word to the picture. For both versions the first 100 items were used; he scored 89/100 for spoken words and 59/100 for written words (a chance score is 25/100). It is thus clear that he displayed a selective written word comprehension deficit on this test.

Experiment 2. Name-Matching. Name matching was tested by using pairs of real words and nonsense words printed in lower and upper case. The real word set comprised 120 high frequency words, there being an equal number of 3, 4 and 5 letter words. A comparable set of 3, 4 and 5 letter non-words were generated, such that the 3 and 4 letter non-words differed from a high frequency word by one letter and the 5 letter non-words differed by 2 letters (in all cases they were pronounceable). For each initial real word a matched real word with only one letter change was generated for the 'different' judgements (e.g. alone/along). Similarly for the non-words there was one letter change for the 'different' judgements (e.g. det/dit). Each pair of real words and of non-words was typed singly on index cards, the first word of the pair being typed in upper case, the second in lower case; the real word pairs and non-word pairs being presented in a random order. AR was required to respond 'same' or 'different' at his own pace, no time limit being imposed. This procedure was repeated with the same set of real words and non-words being written in lower case but each of the pair in different handwriting (TS's and EKW's). The number of correct judgements for each condition is shown in Table 2. Performance was no better than would be expected if he were guessing randomly when no word could be read. For instance, if he performed correctly on any trial where at least one word could be read and otherwise guessed randomly, then a reading rate of 35 per cent (a plausible lower bound) would result in 73 per cent correct performance on this task, a higher value than that actually obtained.

TABLE 2. MATCHING PERFORMANCE (CHANCE = 50 PER CENT)

	Upper/lower case	*Two handwritings*
Words	76/120 (63%)	81/120 (67%)
Non-words	53/90 (59%)	55/90 (61%)

Experiment 3. Lexical Decision. 55 words and 45 non-words were selected from those used in Experiment 2. All stimuli were typed in lower case and presented individually on index cards. For each stimulus AR was required to make a yes/no response as to whether it was a real word. He scored only 64/100 correct (words 26/55 and non-words 38/45). If one assumes that he said 'yes' only if he thought (correctly or incorrectly) that he could read the word, and that such incorrect reading (that is, corresponding to an explicit error) was as frequent for non-words as for words he failed to read correctly, one can predict this result quite closely. Thus, using the overall value of his reading level of 42 per cent correct and 19 per cent errors, one predicts a result of 34/55 for words and 36/45 for non-words. This means that he had no knowledge about whether a word he could not read was a word or not.

Experiment 4. Miming Test. Twenty high frequency action words were typed individually in lower case on index cards. He was able to read aloud 11/20 correctly. He was totally unable to mime the action of the 9 words he was unable to read (tap, hum, knock, bow, point, lift, drag, throw, bend). The appropriate actions were all carried out with verve when the words were presented auditorially. A further miming task was given—AR first attempted to read 50 object names and 50 action words presented in random order. For each word that he was unable to read, he was asked first to categorize it as an object or an action and secondly to attempt a mime appropriate to the word. AR was unable to read 65/100 of this set of words and he was only able to mime 18/65 of the words he was unable to read at first presentation. Moreover, AR was able to read 10 of these words after miming the action. For example, in attempting to mime the word 'kick' (a word he had been unable to read) he commented 'It seems to me I ought to use my feet . . . kicking . . . oh, kick'. Again he had no difficulty with this task with auditory presentation.

Comment. It has been shown that AR's written word recognition was severely impaired: his performance on written word/picture matching tests, miming tests and a name matching task was very poor. Not only was he unable to comprehend the meaning of written words, he was unable to differentiate a word from a non-word with any semblance of accuracy. It is quite clear that his reading difficulties can in no way be accounted for by his very pronounced nominal difficulties.

Partial Comprehension in Reading

Clinical observation suggested to us that AR's failure to recognize words was by no means complete; he often appeared to derive partial information from the written word; for example, in attempting to read the word 'beaver' he commented 'could be an animal, I have no idea which one'. For 'cereal' he said 'it is something you eat'. AR himself commented 'it seems as if I am almost there, but it seems as if I can't go over the last little bit and finally grasp it'. AR's capacities for semantic categorization of the written word were therefore explored. In the following group of experiments AR was first required to read the word or indicate its meaning by giving a verbal descriptive response. For all words that he was unable to comprehend he was immediately presented with the categorization task; he was not asked to categorize words he succeeded in reading or identifying.

Experiment 5. Categorization of Concrete Words. Twenty-five words from each of 5 taxonomic categories (animals, plants, parts of the body, foods and objects) were typed individually in lower case on index cards. He was able to read 34 of the words and indicate the meaning of 4. A two-choice categorization task was immediately given for the remaining 87 words. For example, unable to read or identify 'crocus' he was asked 'Is it an animal or a plant?' He correctly categorized 68 of these 87 words, which is well above chance (43·5 ± 4·7).

Experiment 6. Categorization of Concrete Words Presented Tachistoscopically.

(*a*) A 40 word subset from the pool of words used in Experiment 5 was presented tachistoscopically, alternating between exposure durations of 100 ms and 300 ms.

(*b*) A second subset of 80 words from Experiment 5 was attempted, alternating between a tachistoscopic presentation (300 ms) and unpaced presentation across the desk.

In these two tasks AR first attempted to read the word. Those words he was unable to read he was immediately asked to categorize into one of the five categories used in Experiment 5. The number of words read correctly and categorized correctly for each presentation condition are given in Table 3. In 3 out of the 4 presentation conditions his categorization score was significantly above chance. Presentation time did not appear to have a strong effect on either his ability to read words or his ability to categorize.

TABLE 3. READING AND CATEGORIZATION PERFORMANCE COMPARING DIFFERENT DURATIONS OF EXPOSURE TO STIMULI. EXPERIMENT 6(*a*) AND (*b*)

		Correctly read	*Correctly categorized*	*Chance categorization*
(*a*)	100 ms	5/20	8/15	(3±1·5)
	300 ms	8/20	4/12	(2·4±1·4)
(*b*)	300 ms	7/40	15/33	(6·6±2·3)
	unlimited	8/40	22/32	(6·4±2·3)

Experiment 7. Categorization of Non-concrete Words. AR attempted 5 tasks of categorization of non-concrete words (the procedure described above was used).

(*a*) A set of 30 surnames and 30 forenames likely to be known to AR were selected. Each was typed individually on an index card, the first letter being upper case, and presented singly in random order. AR attempted first to read the name, then to categorize it as a surname or forename. AR's categorization performance on this task was extremely good (*see* Table 4).

(*b*) A set of 30 boys' names and 30 girls' names likely to be known to AR were selected. The procedure was identical to the surname/forename task except that AR attempted to categorize the words as boys' names or girls' names. Subsequently a subset of 20 boys' names and 20 girls' names were shown tachistoscopically using a 100 msec exposure duration. Again categorization performance on these tasks was excellent (*see* Table 4).

TABLE 4. PERFORMANCE ON FIVE NON-CONCRETE CATEGORIZATION TASKS

Word stimuli	*Read*	*Categorization*	*Chance categorization performance*
Surnames/forenames	9/60	49/51	(25·5±3·6)
Boys'/girls' names	1/60	55/59	(29·5±3·8)
Boys/girls 100 ms	2/40	37/38	(19±3·1)
Authors/politicians	14/100	69/86	(43±4·6)
Subject/measurement	12/50	31/38	(19±3·1)

(*c*) A set of 100 well-known politicians and authors (both contemporary and historical figures) likely to be known to AR were selected. Some of these names were in fact quite obscure (Stendhal, Bismarck, Thackeray and Attaturk). The names were typed as above and presented in random order. AR again attempted to read each name and then classified those which could not be read as author or politician. (These names were mostly within his vocabulary since he obtained a score of 93/100 when attempting the same task with auditory presentation.) On this task in particular it is most improbable that orthographic cues could contribute to the categorization of proper names according to occupation, yet again AR scored well above chance (*see* Table 4), correctly categorizing names he could neither read nor describe. On this task he was also asked for further details of those people that he had categorized correctly, but not read. There was a striking inferiority in his ability to provide accurate details with visual presentation when compared with auditory. For instance, *Solzhenitzyn* was judged to be a non-British author who wrote novels with both modes of presentation. However, with visual presentation he was described as being a Pole who died in about 1900; in contrast his description with auditory presentation was of being Russian and still alive. Considering all trials on which naming did not occur and the basic categorization was correctly performed both auditorially and visually, his descriptions were rated as auditory better for 25 names, visual better for 7 names and roughly equally good for 30 names. His auditory performance was significantly superior (Sign Test $P < 0{\cdot}01$).

(*d*) 25 Measurement words and 25 academic subjects (e.g. acre, biology) likely to be known to AR were typed individually on cards and presented to AR as in the above tasks. His categorization performance was well above chance (*see* Table 4).

Experiment 8. Categorization of Superordinate and Subordinate Classes. AR's capacity for semantic categorization of words partially comprehended was further explored by probing recognition of superordinate and subordinate categories. A test was adapted from a procedure devised to probe knowledge of superordinate and subordinate categories in a patient with auditory agnosia (EM, described by Warrington, 1975). For AR the same set of 40 concrete nouns were typed individually in lower case on index cards. Two levels of superordinate category choices followed by 2 subordinate category choices were attempted. The choices for the superordinate categories were:

(1) *animal, plant, inanimate object* (for all items);

(2) *mammal, bird, insect*: *tree, flower, fruit*: *liquid, stone, metal* (as appropriate).

The choices for the subordinate categories were adapted to be appropriate to the item, for example, *cabbage—green, brown, grey*: *walrus, 0, 2* or *4 legs*: *vinegar—sweet, sour, tasteless*: *peach—soft, crisp, juicy,* etc. 20 of the words were tested visually and 20 were tested auditorially. The number of words categorized (omitting words which were correctly read) are given in Table 5. His ability to make the appropriate choice for words he could not read (or identify) was above chance for both the superordinate and subordinate categories. It is of some interest that his performance on the subordinate choice (which appeared to be for him the harder task with auditory presentation), was much the same as for superordinate category choice.

TABLE 5. PERFORMANCE ON VISUAL AND AUDITORY SUPERORDINATE AND SUBORDINATE CATEGORIZATION TASKS

	Number read	*Superordinate categorization*		*Subordinate categorization*		*Chance level*
		Level 1	Level 2	Set 1	Set 2	
Visual	4/20	9/16	9/16	11/16	13/16	5·3±1·9
Auditory		20/20	16/20	12/20	17/20	6·7±2·1

Semantic Priming

In many of the tasks it was occasionally observed that categorization or miming actually led to word-reading. AR would study a word and comment that he did not 'know' it. Subsequently, after he had been guided through the semantic choices, he might identify the word or even read it aloud. It appeared as if the category tasks themselves facilitated his capacity to access the semantic connotation of the written word. The next series of experiments which explored the effectiveness of semantic priming for AR's reading skills derives from these qualitative observations. Two concrete examples may clarify this point:

Turnip—AR incorrectly chose musical instrument from 5 taxonomic categories.

Q. Is it red?

AR. No.

Q. Does it grow below ground?

AR. Yes.

AR. I don't like it whatever it is. Oh, it's turnip.

He categorized 'drum' (which he had been unable to read) as an object. In carrying out the mime, appropriately, he commented 'I seem to imagine I ought to be doing this but I don't know what it is.' Then he said 'drum'.

Two experiments which explore the role of priming for semantic access to the written word were completed: the effectiveness of spoken cues for recognition of written words and for object-naming were compared and the effectiveness for written-word recognition of verbal cues and visual cues were compared.

Experiment 9. The stimulus material comprised 80 clear line drawings of objects (Zinkin and Birtchnell, 1968) and the same 80 object names were typed in lower case, singly on index cards. This experiment was carried out on two separate days and 40 of the stimulus items were used on each occasion. AR first attempted to name the pictures and read the written words, a split half technique being adopted so that half the object names were first attempted from the picture form and half were first attempted from the written word form. AR was tested in blocks of 20 items alternating between pictures and written words. This task was then repeated, AR being given a verbal prompt for each item, the same prompt being used for both the pictorial and written form of the task. For example the prompt for both the picture of a fan and the written word fan was 'for cooling'. The prompt for pyramids was 'Egypt', the prompt for freezer was 'cold', etc.

The number of pictures named and words read with and without a prompt are given in Table 6. The gain given a spoken prompt in terms of numbers of items

TABLE 6. THE NUMBER OF ITEMS THAT CAN BE READ/NAMED IN BOTH THE PROMPT AND NO PROMPT CONDITIONS

		A. *Reading*		
		Without prompt		
		Read	*Failed*	*Total*
With prompt	Read	19	22	41
	Failed	3	36	39
	Total	22	58	80

		B. *Picture Naming*		
		Without prompt		
		Named	*Failed*	*Total*
With prompt	Named	4	14	18
	Failed	3	59	62
	Total	7	73	80

correctly read was greater than the gain in number of pictures named. Spoken prompts significantly increased the number of words read (Sign Test $P < 0{\cdot}01$). Verbal prompts improved reading more than they did picture-naming. To assess this effect it would be inappropriate to compare Tables 6A and 6B directly, as this would be subject to a ceiling effect; a word that has been read or named without a prompt cannot benefit from a prompt in that condition. Therefore, consider those items that could be neither read (as words) nor named (as pictures) without any prompt; the prompt was more likely to facilitate reading than naming (McNemar Test, $P < 0{\cdot}01$, *see* Table 7). As prompts facilitated reading more than they did picture naming, the prompting effect must operate directly on the reading process rather than just be a guessing effect based on the prompt alone.

TABLE 7. THE EFFECT OF A VERBAL PROMPT ON NAMING PICTURES AND READING WORDS, FOR ITEMS THAT COULD NEITHER BE READ NOR NAMED WITHOUT A PROMPT

		Picture Naming		
		Named	*Failed*	*Total*
Word reading	Read	1	19	20
	Failed	4	30	34
	Total	5	49	54

Experiment 10. The test stimuli comprised 80 written words corresponding to the 80 Zinkin pictures described in the previous experiment. AR attempted to read each of these words with either a spoken prompt or a visual prompt. The spoken prompts were identical to those used in Experiment 8 and the visual prompt was the actual Zinkin pictorial representation of the word. Thus in attempting to read the word pyramid AR would have either the spoken prompt (Egypt) or the visual prompt (the picture of the pyramid). Again a double split half technique was adopted and AR was tested in blocks of 20 items, all 80 items being tested with both the spoken and visual prompt. The number of words correctly read with verbal and visual prompts are given in Table 8.

TABLE 8. NUMBER OF ITEMS READ/FAILED WITH THE TWO TYPES OF PROMPT

Both trials	*One trial correct*		*Neither trial*
correct	*Verbal only*	*Picture only*	*correct*
29	20	7	24

It is clear that there was a greater facilitatory effect of a spoken prompt than a visual prompt (Sign Test, $P < 0{\cdot}025$) even though the visual prompt provided, at least at the conceptual level, the complete solution. Having recognized a picture of a pyramid he was less able to use this information than the information contained in the verbal message 'Egypt' to actually read the word 'pyramid'. The implication of this result will be discussed fully later.

DISCUSSION

A patient presenting with the syndrome of dyslexia without dysgraphia has been systematically tested on a series of tasks designed to analyse the basis of his inability to read. It will be argued that AR had a deficit impairing access to the semantic systems involved in reading. The cardinal features of his performance may be listed as follows:

(a) AR's ability to either name or sound individual written letters was severely impaired;

(b) AR's performance on matching upper/lower case letters and words was very poor;

(c) AR's whole word reading skills were reduced to a level in the region of 30 to 50 per cent accuracy and were little affected by the linguistic properties of the word pool. For example, his deficit was relatively unaffected by word concreteness, word length, word frequency or part of speech;

(d) there was a preponderance of visually based errors together with a markedly low incidence of semantic derivational errors;

(e) AR demonstrated a very striking capacity to categorize, according to their taxonomic categories, words which he failed to read;

(f) verbal semantic priming had a facilitatory effect on AR's residual reading capacity.

The major interest of this investigation concerns the operation of the direct route for reading, but it is necessary first to demonstrate that other possible strategies for comprehension of the written word were not available. In view of the recent interest in the syndromes involving the failure of phonological reading (Marshall and Newcombe, 1966; Shallice and Warrington, 1975; Patterson and Marcel, 1977; Saffran and Marin, 1977) it then becomes appropriate to compare AR's residual reading capacities with those of previously reported phonemic/deep dyslexics.

We would argue that for AR phonological reading was not viable. His ability to name or sound individual letters was impaired and his ability to read three-letter nonsense syllables was very poor. His performance on these tasks appeared to be commensurate with his letter reading skills. Some indication of the severity of his letter reading difficulty was demonstrated by his very poor performance on the lower and upper case matching tasks—he had comparable difficulty with matching pairs of letters, real words and nonsense words. These tasks could obviously be mediated by a phonological transformation (though in the case of real words, the task could in addition be achieved by the direct visual form/semantic route). That is, any patient with either the capacity to name or to sound individual written letters, even though reading whole words was faulty, could do this task. Clearly AR had an additional or perhaps more basic deficit, the impairment of single letter recognition. Not only could he neither name nor sound written letters reliably but he did not recognize that *H* and *h* were two forms of the same symbol. We would argue that this failure in recognition precludes the operation of the phonological route, whether or not the route is itself damaged. It is possible that AR's phonological route was not itself damaged but merely rendered inoperative by his recognition deficit. The fact that performance on other tasks which can be assumed to have a phonological component, such as spelling, was relatively normal is suggestive in this respect. There was also a somewhat different pattern of word reading errors. Derivational errors were less common for AR than is usually the case in phonemic/deep dyslexic patients. This observation could be adduced to support Patterson's speculation that root morphemes are read by the direct word form/semantic route, but that the precise form involving bound morphemes requires the phonological route to be intact.

Whether his phonological reading system was damaged or merely inaccessible it is the partial preservation of his reading directly for meaning, which is of intrinsic interest and provides the main focus of the present investigation. Firstly, it is necessary to consider whether peripheral factors could contribute to his inability to recognize letters and words, that is, whether visual processing prior to and including the visual word form was abnormal. This seems unlikely to be the case. It was demonstrated that there were no visual interference effects, no visual neglect, nor any sizeable word length effect. More important, there was no evidence to suggest that tachistoscopic presentation reduced his reading skills. Both his absolute level of reading and his capacity for word categorization were relatively unaffected by tachistoscopic exposures as short as 100 ms. As tachistoscopic presentation can be assumed to rely normally on whole word reading, we would argue that his ability to achieve a word form was not impaired.

The major finding of this investigation was the substantial preservation of AR's capacity for semantic categorization of words that he failed to comprehend. AR had virtually no difficulty in differentiating girls' names from boys' names, and surnames from forenames, whether presented tachistoscopically or not. Even politicians and authors could be categorized with reasonable success. Many other examples of semantic categorization are reported in Experiments 6 to 9. A similar phenomenon may have occurred for letters. AR's ability to read individual letters was very impaired. Nevertheless, he could categorize letters according to their order in the alphabet relatively well.

It is clear that this striking phenomenon is not a trivial consequence of his nominal dysphasia. Upper/lower case matching tasks should present no difficulty if his deficit were merely at the response output level. On written word-picture matching tests his performance, though above chance, was very impaired. He was not able to mime the precise action of written words he had successfully categorized as actions. On these two tasks, auditory presentation of the same words led to far superior performance. In the case of authors/politicians it was possible to establish by probing additional information that the person had not in fact been identified. It is also worth noting that his categorization skill is unlikely to have been mediated by visual imagery, since his ability to differentiate surnames from forenames was particularly good.

It appears then that AR could often achieve partial comprehension of written words. This being the case it seems reasonable to infer that his letter and word recognition deficit falls within the domain of semantic processing systems. Two partially independent questions arise concerning the nature of this semantic deficit. First, is the deficit due to a general degrading of the relevant semantic memory system *or* is it due to a difficulty in accessing the full semantic representation of the word? Second, is the semantic memory system involved either modality or material specific?

We will consider first the problem of the operation of the semantic memory processes implicated in the present case. Our distinction between the degradation of stored information and the accessing of stored information was motivated by the differences between AR's semantic system deficit and that of patients with a selective impairment of word and object meanings (associative agnosia) reported by Warrington (1975). Therefore we will attempt to describe the properties of access and degradation deficits by contrasting the characteristics of these two syndromes.

There are four findings which suggest that a semantic access deficit is the more appropriate formulation of AR's semantic processing deficit, rather than a degradation phenomenon. First, word frequency did not appear to be an important factor in determining AR's reading skills. Indeed there were many instances of his success in reading or categorizing low frequency items whilst failing high frequency items. Frequency is a major determinant of many aphasic phenomena, and furthermore it was a major influence on the performance of the agnosic patients referred to above, for whom it was argued that there was damage to the stored semantic information. Secondly, the consistency of AR's reading responses was shown to be low; his success in reading words at one time was no guide to his performance later. In contrast there was a very high degree of consistency in the agnosic patients, their performance remaining constant for items of individual stimulus over relatively long periods of time (E. K. Warrington, unpublished).

Third, there was no indication that superordinate information was less vulnerable than subordinate information. AR was able to categorize words which he could not read, equally successfully for superordinate and subordinate categories. In previous studies of patients with auditory word meaning deficits it was argued from the invariant greater vulnerability of subordinate information (fine grain semantic details) compared with superordinate information (broad category knowledge), that there was damage or loss to the central representation itself, resulting in the degradation of stored semantic knowledge. Conversely, in the present case one may speculate that categorization by subordinate features gains in being in some way 'closer' to the target. Finally, the priming effects reported in Experiments 9 and 10 would not be predicted by a degradation hypothesis. Though these priming techniques have not yet been applied to patients with auditory word agnosia, there are a number of clinical observations which suggest these priming effects would not have occurred in the agnosic patients referred to above. For example in their records there is no instance of a correct category judgement leading to the identification of an unknown word, as was often the case with AR.

We would therefore argue that associative agnosia is a deficit of semantic memory which can be characterized by the degradation of stored information. Further, these four different sources of evidence for AR which clearly weigh against the degradation hypothesis are, however, all compatible with an *access* deficit. Indeed the consistency result and the priming results would be predicted by the access hypothesis. The hypothesis that the accessing of the semantic representation of words does not have an 'all-or-none' character, but is a complex process that can be partially disturbed, may seem counter-intuitive. However, if the more specific aspects of word meaning can be lost, with broad category information preserved as occurs in agnosia, then the structure mediating word meaning must be ordered in its degree of specificity, and it becomes plausible that this ordering is reflected in the access process. Hodgkin (1977) has produced evidence in normal subjects for a somewhat similar position, namely that the identification of the meaning of a word involves an interpretive process which takes time and is strongly subject to context effects.

The second issue concerns the possible existence of modality specific meaning systems. This possibility has been advanced previously on the basis of other neuropsychological data (Warrington, 1975). The two experiments exploring the role of semantic priming provide some further evidence for the dissociation of verbal and visual object meaning systems. If a semantic system common to all modalities were being accessed then verbal prompts would be expected to have equivalent effects on object naming and word reading. As was shown in Experiment 9 verbal prompts have much more effect on word reading. Similarly, written word reading would be expected to be prompted as well by a picture of the object as by an auditory verbal prompt, since a picture would seem the closest possible cue. It was shown in Experiment 10 that auditory verbal prompts were the more effective. The prompting experiments, then, support the idea of at least partially independent semantic systems subserving object recognition and word comprehension.

The possibility of the dissociation of meaning systems corresponding to the written and spoken word is less clear-cut. The orthodox explanation of AR's inability to comprehend the written word with auditory comprehension intact would be in terms of disconnection theory. Therefore before attempting to justify the assumption of a partially independent meaning system for the written word, the adequacy of the disconnection interpretation must be discussed. There are a number of findings which suggest that AR's deficit cannot be attributed to a failure in the transmission of information from the visual systems in the right hemisphere (he had a complete right homonymous hemianopia) to language systems in the left hemisphere, the classical explanation of dyslexia without dysgraphia (*see* Dejerine, 1892; Benson and Geschwind, 1969). First, there is evidence that the visual processing resulting in a word-form (a relatively early stage in the reading process), is subserved by the left hemisphere. Patients exist with lesions restricted to very posterior regions of the left hemisphere who appear to have a damaged visual word-form (Warrington and Shallice, 1978). If one assumes that the word-form must precede recognition for meaning it is clear that AR must have had a more central deficit since skills dependent on the word-form appear not to have been impaired. Furthermore, it is now known that a right homonymous hemianopia is not a necessary concomitant of dyslexia without dysgraphia (Greenblatt, 1973).

A more important argument can be derived from AR's capacity to categorize words he was unable to read. This phenomenon, together with the priming effects, directly implicates a deficit within the domain of semantic processing. These phenomena would not have been predicted by an existing disconnection hypothesis nor can they be easily accommodated by a disconnection interpretation. Albert *et al.* (1973) recognize the problem that evidence of some preservation of semantic categorization presents for a disconnection theory, but nevertheless they do not in fact question this class of explanation for the phenomenon. The disconnection view would have to be broadened to the extent of either postulating the existence of category specific connections between the right and the left hemisphere which in turn implies that some considerable semantic categorization is achieved by the right hemisphere, or that there is a partial disconnection within the left hemisphere of the word-form from the semantic system. If a hypothetical right hemisphere system were implicated then other characteristics imputed to the right hemisphere, such as a difficulty with function words and an abstract/concrete difference, could have been expected (Marcel and Patterson, 1978). In any case, there is no unequivocal evidence that the right hemisphere plays any significant role in semantic processing and indeed in a different context it has been claimed that the right hemisphere is implicated at the level of perceptual and not semantic processing (Warrington and Taylor, 1978).

The most plausible but entirely *ad hoc* reformulation of the disconnection hypothesis requires postulating a partial disconnection within the left hemisphere between the visual word-form and semantic systems. It could then be held that partial semantic processing is the result of a 'weak' input being received by the semantic system from the visual word-form system (Shallice and McGill, 1978).

However, even in situations where such 'weak' input may be expected to occur—such as pattern masking—the semantic effects are relatively minor (Shallice and McGill, 1978; Allport, 1977; Marcel, 1974; Ellis and Marshall, 1978). The magnitude of the semantic categorization effects reported, together with the speculative nature of this explanation, render even this extension of the disconnection explanation of AR's reading difficulties implausible.

If a disconnection explanation is rejected, the very existence of a selective written word comprehension deficit is *prima facie* evidence for a meaning system, or at least access to its semantic representation, partially specific to the written word. One piece of evidence provides some but very tentative support for this thesis. Close auditory verbal cues only increased AR's reading performance from 22/80 to 41/80, which is not a strong effect, given his good auditory comprehension and his performance on the test of naming words from their description. If an access system common to both modalities were being used, one might have expected near perfect performance since very little stimulus information should be required from the written word for reading.

It would be premature to attempt a detailed theory of all aspects of AR's dyslexic difficulties. Recent neuropsychological investigations have brought to light the heterogeneity of the acquired dyslexia syndromes (Shallice and Warrington, 1979). The similarities and differences between AR and previously reported patients with phonemic dyslexia make it clear that not even a satisfactory taxonomy of the acquired dyslexias has yet been put forward.

The potential implications of the very surprising phenomenon of partial and gradual attainment of written word meaning observed in AR appears to us important. It seems distinctly possible that the accessing of word meaning in normal subjects follows a similar but more rapid course. The precise meaning of a word may well be accessed only as the end result of a process which involves the attaining of increasingly specific semantic representations.

SUMMARY

An analytical investigation of the residual reading capacities of a single patient with dyslexia without dysgraphia is reported. Both his ability to name and to comprehend letters and words were severely impaired. The major finding of this investigation was AR's striking capacity for categorizing words he could not read. In addition there was evidence of semantic priming effects. Thus AR was frequently able to achieve partial comprehension of words he could not read. The orthodox interpretation of the dyslexia without dysgraphia in terms of a disconnection syndrome is shown to be inappropriate, at least for the present case, where the deficit appears to be within the semantic domain; it is argued that this type of dyslexia is due to an impairment in accessing semantic information.

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REFERENCES

ALBERT, M. L., YAMADORI, A., GARDNER, H. and HOWES, D. (1973) Comprehension in alexia. *Brain*, **96**, 317-328.

ALLPORT, D. A. (1977) On knowing the meaning of words we are unable to report: the effects of visual masking. In: *Attention and Performance.* VI. Edited by S. Dornic. London: Academic Press.

BENSON, D. F. and GESCHWIND, N. (1969) The alexias. In: *Handbook of Clinical Neurology.* Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, Vol. 4, pp. 112-140.

BROWN, W. P. and URE, D. M. N. (1969) Five rated characteristics of 650 word association stimuli. *British Journal of Psychology*, **60**, 223-250.

COUGHLAN, A. and WARRINGTON, E. K. (1978) Word-comprehension and word-retrieval in patients with localized cerebral lesions. *Brain*, **101**, 163-185.

DEJERINE, J. (1892) Contribution à l'étude anatomoclinique et clinique des différentes variétés de cécité verbale. *Compte Rendu Hebdomadaire des Scéances et Memoires de la Société de Biologie*, **4**, 61-90.

ELLIS, A. W. and MARSHALL, J. C. (1978) Semantic errors or statistical flukes? A note on Allport's 'On knowing the meaning of words we are unable to report'. *Quarterly Journal of Experimental Psychology*, **30**, 569-575.

FREUND, D. C. (1889) Über optische Aphasie und Seelenblindheit. *Archiv für Psychiatrie und Nervenkrankheiten*, **20**, 276-297.

GREENBLATT, S. H. (1973) Alexia without agraphia or hemianopsia. *Brain*, **96**, 307-316.

HÉCAEN, H., GOLDBLUM, M. C., MASURE, M. C. and RAMIER, A. M. (1974) Une nouvelle observation d'agnosie d'objet. Deficit de l'association ou de la categorization, specifique de la modalité visuelle? *Neuropsychologia*, **12**, 447-464.

HODGKIN, E. D. (1977) An experimental study of semantic comprehension and semantic memory. Unpublished Ph.D. Thesis, University of London.

KATZ, J. J. and FODOR, J. A. (1964) The structure of a semantic theory. *Language*, **39**, 170-210.

LHERMITTE, F. and BEAUVOIS, M. F. (1973) A visual-speech disconnection syndrome: report of a case with optic aphasia, agnosic alexia and colour agnosia. *Brain*, **96**, 695-714.

MARCEL, A. J. (1974) Perception with and without awareness. Paper presented to the Experimental Psychology Society, Stirling.

—— and PATTERSON, K. (1978) Word recognition and production: reciprocity in clinical and normal studies. In: *Attention and Performance. Vol. VII.* Edited by J. Requin. New Jersey: Lawrence Erlbaum.

MARSHALL, J. C. and NEWCOMBE, F. (1966) Syntactic and semantic errors in paralexia. *Neuropsychologia*, **4,** 169–176.

—— —— (1973) Patterns of paralexia: a psycholinguistic approach. *Journal of Psycholinguistic Research*, **2,** 175–199.

PAIVIO, A., YUILLE, J. C. and MADIGAN, J. A. (1968) Concreteness, imagery and meaningfulness values for 925 nouns. *Journal of Experimental Psychology*. Supplement, **76,** 1–25.

PATTERSON, K. E. and MARCEL, A. J. (1977) Aphasia dyslexia and the phonological coding of written words. *Quarterly Journal of Experimental Psychology*, **29,** 307–318.

ROMMETVEIT, R. (1968) *Words, Meanings and Messages*. London: Academic Press.

SAFFRAN, E. M. and MARIN, O. S. M. (1977) Reading without phonology: evidence from aphasia. *Quarterly Journal of Experimental Psychology*, **29,** 515–525.

SCHWARTZ, M. F., MARIN, O. S. M. and SAFFRAN, E. M. (1979) Language and reference in dementia: a case study. *Brain and Language*. In press.

SHALLICE, T. and MCGILL, J. (1978) The origins of mixed errors. In: *Attention and Performance. Vol. VII.* Edited by J. Requin. New Jersey: Lawrence Erlbaum.

—— and WARRINGTON, E. K. (1975) Word recognition in a phonemic dyslexic patient. *Quarterly Journal of Experimental Psychology*, **27,** 187–199.

—— —— (1979) Single and multiple component central dyslexic syndromes. In: *Deep Dyslexia.* Edited by M. Coltheart, K. E. Patterson and J. C. Marshall. London: Routledge. In press.

TAYLOR, A. and WARRINGTON, E. K. (1971) Visual agnosia: a single case report. *Cortex*, **7,** 152–161.

THORNDIKE, E. L. and LORGE, I. (1944) *The Teacher's Word Book of 30,000 Words.* New York: Teachers College.

WARRINGTON, E. K. (1975) The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, **27,** 635–657.

—— and SHALLICE, T. (1978) Spelling dyslexia: impairment of the visual word-form. *Experimental Brain Research*, **32,** R50.

—— and TAYLOR, A. M. (1978) Two categorical stages of object recognition. *Perception.*

ZINKIN, S. and BIRTCHNELL, J. (1968) Unilateral electroconvulsive therapy: its effects on memory and its therapeutic efficacy. *British Journal of Psychiatry*, **114,** 973–988.

(*Received March 28, 1978*)

Brain (1979), **102**, 65-77

NEUROFIBRILLARY DEGENERATION ON GUAM

FREQUENCY IN CHAMORROS AND NON CHAMORROS WITH NO KNOWN NEUROLOGICAL DISEASE

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INTRODUCTION

THE phenomenal incidence of parkinsonian dementia and amyotrophic lateral sclerosis on Guam remains unexplained (Hirano, Kurland, Krooth and Lessell, 1961*a*; Brody, Stanhope and Kurland, 1975). The most objective pathological abnormality in parkinsonian dementia besides the loss of neurons in the substantia nigra is the presence of neurofibrillary degeneration in neurons of the cerebral cortex, subcortical nuclei and brain-stem (Hirano, Malamud and Kurland, 1961*b*). Clinically apparent parkinsonian dementia has been shown to be associated with severe neurofibrillary degeneration in all cases. As shown, however, by preliminary studies, some Guamanians with no known neurological disease have some degree of neurofibrillary degeneration on post-mortem examination (Hirano, Malamud, Elizan and Kurland, 1966; Brody, Hirano and Scott, 1971). The purpose of this paper is to demonstrate the frequency of neurofibrillary degeneration in Guamanian patients without known dementia, parkinsonism or amyotrophic lateral sclerosis. The frequency of neurofibrillary degeneration in these patients has also been looked at with regard to age, sex, village of birth and residence prior to death, and presence of amyotrophic lateral sclerosis or parkinsonian dementia in siblings or parents. Other investigators (Gellerstedt, 1933; Malamud, 1965; Matsuyama, Namiki and Watanabe, 1966; Tomlinson, 1968;

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Dayan, 1970*a*; Forno and Alvord, 1971) have reported the age-related incidence rates of neurofibrillary degeneration in 'control' populations in different races and from different parts of the world. Our data will also be compared with these studies.

MATERIAL AND METHODS

The 69 patients included in the Chamorro study consisted of 37 males and 32 females dying between the ages of 16 and 100 years without known dementia, parkinsonism or amyotrophic lateral sclerosis. All these patients were residents of Guam of Chamorro descent. The patients came from the acute medical wards of the Guam Memorial Hospital, the US Naval Hospital, Guam, or were dead on arrival at the Guam Memorial Hospital. None of the patients were from the mental wards.

The causes of death based upon a review of the available clinical histories and autopsy reports were determined to be as follows: acute and chronic cardiovascular disease (25); carcinoma (13); accidental (trauma or drowning, 10); tuberculosis (4); pneumonia (3); acute cerebrovascular accident (3); renal failure (2); myocarditis (1); pulmonary hæmorrhage (1); ruptured abdominal aortic aneurysm (1); hæmorrhagic pancreatitis (1); meningitis (1); hepatic failure (1); unknown (3).

None of the patients in this study had clinically diagnosed parkinsonian dementia. Virtually all patients with parkinsonian dementia sufficiently advanced to be recognized are known at the NINCDS Research Center. The Research Center was established on Guam in 1956 for the purpose of identifying and studying all cases of parkinsonian dementia and amyotrophic lateral sclerosis. Medical and paramedical personnel on Guam have consistently been extremely co-operative in referring patients to the Center. The patients and their families have an incentive for their being seen, since they receive free medical care and medication once they are entered in the Research Center Registry. Since 1970 routine treatment includes levodopa which ameliorates the extrapyramidal features in most instances.

The brains of 8 Caucasian males who had been longtime residents of Guam were also available for examination. All these patients had been living in the community and had no overt neurological or psychiatric disease.

In all cases, the brain was fixed in formaldehyde solution. A set protocol was followed with sections being taken, in most cases, from the following regions: cerebral cortex (superior frontal, orbital, anterior temporal, parietal and occipital), thalamus, hypothalamus, basal ganglia, hippocampus, midbrain, pons, medulla and cerebellum. The stains used were hæmatoxylin-eosin and the Bodian silver-impregnation method.

The extent of neurofibrillary degeneration was graded for all of the sections on the basis of the following scale, which, although of necessity arbitrary and lacking in quantitative precision, corresponds generally with what others have used. *None*: We have considered that 1 to 3 scattered neurons with neurofibrillary tangles throughout the entire set of sections were equivalent to none at all. *Mild*: Rarely more than a single neurofibrillary tangle in a field, but a number of fields with neurofibrillary tangles (a field is the area visible at 100 × magnification). *Moderate*: Frequently more than one neurofibrillary tangle per field, and most fields contain neurofibrillary tangles, but with many normal cells still remaining. Sometimes very many neurofibrillary tangles in a few limited areas, with some areas with only mild changes. *Severe*: Majority of cells with neurofibrillary tangles in many areas. The grading of the sections was carried out in all the cases by one of us (F.H.A.), and in the majority by two of us (F.H.A. and H.O.) independently. There was good agreement between these two observers as to the grade of severity assigned.

RESULTS

Neurofibrillary Degeneration

When neurofibrillary tangles occurred, distribution throughout the brain in these Guamanian control cases corresponded closely with that described by Hirano *et al.* (1961*b*, 1962) in the brains from patients with parkinsonian dementia of Guam. The regions affected were the hippocampal gyrus (especially the glomerular formation and Sommer's sector), the amygdaloid nucleus, hypothalamus, substantia innominata, locus caeruleus, cerebral cortex (temporal more than frontal), peri-aqueductal gray matter, median raphe, and substantia nigra. In a few cases of severe involvement, very occasional neurofibrillary tangles were seen in the putamen, basis pontis and dentate nucleus. In no case were neurofibrillary tangles seen in the caudate, globus pallidus, thalamus, parietal-occipital cortex, red nuclei, olivary nuclei, or the Purkinje cells of the cerebellum. The hippocampal gyrus, on the other hand, regularly showed a degree of involvement that either was greater than, or at least as severe as, that found in other parts of the brain. In one case, mild neurofibrillary degeneration was present in the brainstem and not elsewhere (midline medullary tegmentum). In one case in which there was moderate involvement in the hippocampal gyrus, there was severe involvement in the locus caeruleus. Moderate involvement of the locus caeruleus alone, with no neurofibrillary tangles seen elsewhere, occurred in 2 cases.

In Table 1 the number of cases in each age group are listed according to the severity of neurofibrillary degeneration in the various parts of the brain. The locus caeruleus is dealt with separately because of the report by Forno and Alvord (1971) that neurofibrillary degeneration was found in this nucleus at an early age in 330 cases without parkinsonism. In Table 2, the data from Table 1 are expressed as the percentage of cases showing involvement in relationship to age and region of the brain. Table 3 shows the frequency of neurofibrillary degeneration in other cortical areas if the hippocampus is affected.

Substantia nigra. In 36 controls and 12 clinically diagnosed cases of parkinsonian dementia from Guam, adequate sections of the substantia nigra were available for comparison. In 50 per cent (6/12) of the parkinsonian dementia cases, there was nearly total disappearance of the pigmented neurons while none of the control cases showed neuronal depletion to this extent. In the remaining 50 per cent (6/12) of the parkinsonian dementia cases, the neuronal loss was less severe but was clearly apparent; a similar degree of neuronal loss was seen in 11 per cent (4/36) of the control cases. Eighty-nine per cent (32/36) of the control cases showed no appreciable loss of neurons in the substantia nigra, while none of the cases of parkinsonian dementia had normal numbers of neurons in this region.

Senile plaques. In 67 of the 69 cases, the sections were judged to be sufficiently well stained and comprehensive to be assessed for the presence of senile plaques. These were found in only 6 out of the 67 cases. They were few in number and were limited to the hippocampal region.

Table 1. Neurofibrillary Degeneration in Guamanian Controls

Age (*yrs*)	*All areas except locus caeruleus*				*Hippocampal area*				*Cortex except hippocampal area*				*Locus caeruleus*				*Brain-stem excluding locus caeruleus*			
	0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+
10–19	5	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0	5	0	0	0
20–29	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
30–39	5	1	1	0	5	1	1	0	5	1	1	0	3	1	1	0	5	1	1	0
40–49	6	2	2	0	6	2	2	0	7	2	1	0	7	1	1	0	7	1	1	0
50–59	8	3	0	5	9	2	0	5	7	3	2	3	7	1	3	2	7	4	3	1
60–69	3	0	4	4	3	0	4	4	5	0	3	3	4	3	1	2	5	4	1	1
70–79	1	3	4	3	1	3	4	3	5	4	0	1	5	2	2	0	7	2	1	0
80–89	0	0	1	5	0	0	1	5	1	2	2	1	3	0	2	1	1	0	4	1
90–100	1	1	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1	1	0	0

No. of cases grouped according to age and region of the brain. 0 = None, 1+ = Mild, 2+ = Moderate, 3+ = Severe (*see* text).

Table 2. Percentage of Cases with Neurofibrillary Tangles in Guamanian 'Controls' by Age

Age (yrs)	*All areas except locus caeruleus*	*Hippocampal area*	*Cortex except hippocampal area*	*Locus caeruleus*	*Brain-stem except locus caeruleus*
10–19	0	0	0	0	0
20–29	0	0	0	0	0
30–39	29	29	29	40	29
40–49	40	40	30	28	22
50–59	50	45	45	46	53
60–69	73	73	55	60	55
70–79	91	91	50	44	30
80–89	100	100	83	50	83
90+	50	50	50	50	50

Brain weight. The weight of the brain at autopsy was available in 16 of 69 control cases. When the brain weights in the cases showing moderate to severe neurofibrillary degeneration were compared with those reported by Hirano *et al.* in 17 parkinsonian dementia cases, some overlap in weights was noted but the difference in the median brain weights was significant; that of the parkinsonian dementia cases was 1000 g (range 860 to 1310), and that of the 8 controls with moderate to severe changes was 1278 g (range 1120 to 1500).

Neurofibrillary Degeneration in Caucasians Residing on Guam

Six men between the age of 45 and 64 years with the longest residence on Guam showed no neurofibrillary degeneration. A man aged 72, who had spent his last five years on Guam, showed moderate neurofibrillary degeneration in the brain-stem and mild neurofibrillary degeneration in the hippocampal area with no senile plaques in any of the sections studied. A man aged 74, who had spent his last four years on Guam, showed moderate neurofibrillary degeneration in the hippocampal area and cerebral cortex, mild neurofibrillary degeneration in the brain-stem, and severe senile plaque formation throughout the cerebral cortex.

Table 3. Frequency of Neurofibrillary Degeneration in Other Cortical Areas if Hippocampus Affected (Guam Material)

Hippocampal neurofibrillary degeneration	*Percentage of cases with involvement in other cortical areas*
Mild	67% (6/9)
Moderate	67% (8/12)
Severe	94% (15/16)
Total	78% (29/37)

TABLE 4. NEUROFIBRILLARY DEGENERATION IN GUAMANIAN CONTROLS

All areas except locus caeruleus

	0	1+	2+	3+	*Total*
Male	16	6	6	9	37
Female	14	4	6	8	32

(No. of cases grouped according to sex) (*see* Table 1)

Sex

The presence or severity of neurofibrillary degeneration was not significantly different between males and females, either with respect to age of occurrence or regional localization in the brain. (*See* Table 4.)

Village of Birth and Village of Residence

Epidemiological studies (Brody *et al.*, 1975; Reed *et al.*, 1975*a*, *b*) have shown that certain southern villages on Guam have the highest incidence rates of amyotrophic lateral sclerosis and parkinsonian dementia, the western villages have the lowest rates, and the central and northern villages have intermediate rates. In order to determine whether there was any correlation between subclinical neuropathological disease (neurofibrillary degeneration) and the incidence of clinical disease, the cases under study were grouped based on the above geographical areas. Of the 69 deaths studied the village of birth was known for 55 (*see* Table 5). The percentage frequency of neurofibrillary degeneration for the low, middle and high rate villages were 50, 70 and 70. The village of residence was known for 61 and the

TABLE 5. CORRELATION BETWEEN SUBCLINICAL NEUROPATHOLOGICAL DISEASE (NFT) AND THE INCIDENCE OF CLINICAL DISEASE BY GEOGRAPHICAL REGIONS ON GUAM

Village of Birth

Incidence rate of village	*Low*	*Middle*	*High*
Average age	61·5	60·2	61·7
Median	58	63	58
Range	42–91	35–81	39–100
Percentage with NFT	(6/12) 50%	(23/33) 70%	(7/10) 70%

Village of Residence

Incidence rate of village	*Low*	*Middle*	*High*
Average age	60·2	57·2	66·6
Range	42–91	35–81	39–100
Median	58	57	59
Percentage with NFT	(6/13) 46%	(23/37) 62%	(8/11) 73%

corresponding percentage frequencies were 46, 62 and 73. In both these classifications the size of the subgroups are very small. Although the sample results suggest the same positive association with amyotrophic lateral sclerosis–parkinsonian dementia rates shown by the clinical epidemiological studies, the evidence is not sufficient to justify the conclusion that the true rates show a similar association.

Similarly, the differences in the percentage of neurofibrillary degeneration among those controls with and without a first degree relative with amyotrophic lateral sclerosis or parkinsonian dementia were not significant (Table 6).

TABLE 6. FREQUENCY OF NFT IN CASES WITH AND WITHOUT FAMILY HISTORY FOR AMYOTROPHIC LATERAL SCLEROSIS OR PARKINSONIAN DEMENTIA

	Positive family history	*Negative family history*
Average age	60·3	58·6
Median	57	58
Range	39–80	35–100
Frequency	7/10	28/48
Percentage	70	58

DISCUSSION

This paper has described the occurrence of Alzheimer's neurofibrillary tangles among 69 Guamanians of Chamorro descent who had no known parkinsonism, dementia or amyotrophic lateral sclerosis.

Gellerstedt (1933) examined the brains of 50 patients who died between the age of 65 and 97 years and who were thought to be mentally and neurologically normal. Eighty-two per cent (41/50) showed neurofibrillary degeneration (age-specific incidence rates were not available). Malamud (1965) studied the brains from 75 patients ranging in age from 60 to 84 years and who were not considered 'mentally or neurologically disabled'. He found that only 4 per cent (3/75) showed 'senile changes', which included neurofibrillary change just as one of the types of senile change.

Matsuyama *et al.* (1966) recorded an age-related occurrence of neurofibrillary degeneration in 680 brains from patients in Japan with no known clinical history of psychosis (*see* fig. 1). 'Brains from patients suffering from psychosis and other diseases known to predispose to Alzheimer's neurofibrillary change and senile plaque formations were excluded'. Four hundred were from Tokyo, 236 from Hiroshima and 44 from Nagasaki. The authors specifically state that there was no significant difference in the rate of senile plaques between brains removed from individuals dying in the Tokyo area and those from individuals dying in the Hiroshima and Nagasaki areas. However, they do not comment on whether any difference exists in the frequency of tangles between these geographical areas.

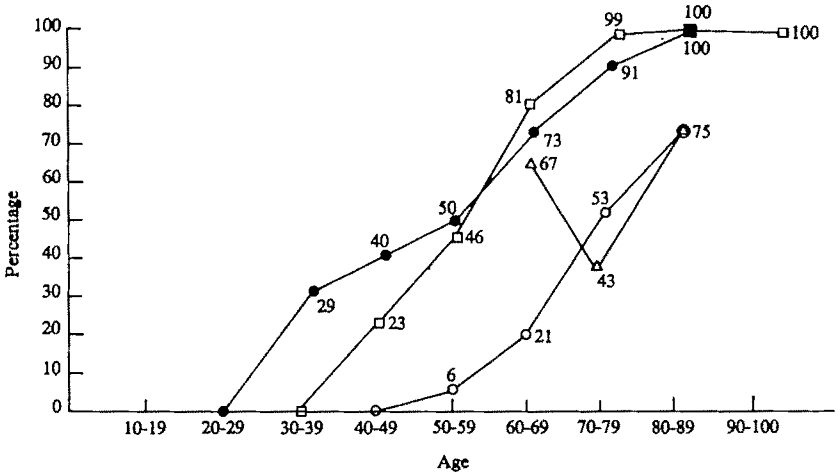

FIG. 1. Frequency (percentage) of neurofibrillary degeneration in control populations. ● Guam, □ Japan (Matsuyama *et al.*, 1966), △ England (Tomlinson *et al.*, 1968), ○ England (Dayan *et al.*, 1970*a*).

Tomlinson, Blessed and Roth (1968) in Newcastle, England, studied the brains of 28 patients ranging in age from 65 to 92 years (mean age of 75 years) considered to be 'well-preserved intellectually' shortly before death. They found neurofibrillary degeneration to be present in 17 out of 28 cases. The age-specific incidence of neurofibrillary tangles is listed in fig. 1. In only 3 of the 17 affected cases were these found in areas of cortex outside the hippocampus and hippocampal gyrus. In another British study, from London, Dayan (1970*a*) examined 75 brains from patients dying 'acutely' from accidental or cardiovascular causes from aged 6 months to 94 years. In order to quantify his data he counted the frequency of senile plaques and neurofibrillary tangles. He found that the chance of an individual patient having neurofibrillary tangles increased with increasing age but that once these changes were present, the severity of involvement did not significantly correlate with age.

Fig. 1 demonstrates that among those populations in which brains were collected over a wide age span, neurofibrillary degeneration appears at an earlier age in the Guamanian population than in the Japanese population and at a much earlier age than in the two English populations.

A number of other investigators have studied the frequency of neurofibrillary tangles in patients with known intellectual impairment.

In an early study of a population of 50 Japanese individuals in the age range of 60 to 88 years with and without dementia, Kin (1942) showed neurofibrillary degeneration in all of the cases although in some the changes were very mild. Two patients, both 57 years old, did not show neurofibrillary degeneration.

Newton (1948) reviewed the frequency of neurofibrillary degeneration in 150 autopsies at a mental hospital. Corsellis (1962) reported the age-related incidence of neurofibrillary change in 207 patients in a mental hospital with diagnoses both of 'organic' and of 'functional' disorders. Wildi, Linder and Costoulas (1964) described the frequency of neurofibrillary degeneration in the brains of 606 psychiatric patients. Tomlinson *et al.* (1970) studied 50 brains of patients who, on the basis of psychological testing, were thought to be demented. Dayan (1970*b*) found neurofibrillary tangles in all 40 cases diagnosed clinically as 'senile dementia' from a population of 'long-stay patients at two large psychiatric hospitals'. Excluded from his study, however, were all cases in which other possible causes of dementia, such as grossly visible cerebral vascular disease or neoplasm anywhere in the body, were present. The results of these studies are summarized in fig. 2.

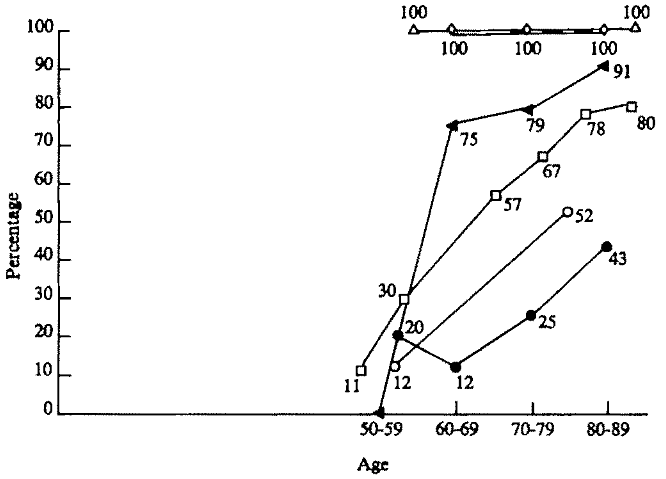

FIG. 2. Frequency (percentage) of neurofibrillary degeneration in populations with known intellectual impairment. ● Corsellis (1962), ○ Newton (1948), □ Wildi *et al.* (1964), ◇ Dayan (1970*a*), ◀ Tomlinson *et al.* (1968), △ Kin (1942).

These six studies illustrate the great variation in frequency of neurofibrillary degeneration found in different case series with known intellectual impairment. A superficial analysis of these data would lead to the conclusion that neurofibrillary degeneration was not related closely with dementia. However, both Dayan and Tomlinson *et al.* noted differences between their demented and non-demented groups. Tomlinson *et al.* found that neurofibrillary change was present 'in both controls and dements in the hippocampus, but elsewhere in the cortex was only severe or widespread in the dements . . .'. Dayan found that 'there is a definite difference between the demented and normal patients in the numbers of neurofibrillary tangles' in the frontal cortex and Ammon's horn. Furthermore, Hirano *et al.* (1961*b*) has found severe widespread neurofibrillary degeneration in addition to moderate to severe degeneration of the substantia nigra, in all cases of parkinsonian dementia of Guam.

A remarkable feature of Guamanian parkinsonian dementia cases as well as our controls is the relative absence of senile plaques (Hirano *et al.*, 1961*b*). Plaques were present in all 40 of Dayan's (1970*b*) selected cases of senile dementia and in 42 of the 50 demented old people studied by Tomlinson *et al.* (1970). In Dayan's (1970*b*) control group, 17 of 47 patients over 60 years of age had plaques. In the study by Tomlinson of 28 non-demented old people (over 65 years old), at least a few plaques were found in 22 cases. Senile plaques were found in only 6 of our 67 Guam 'control' cases (in 4 of 30 over the age of 60 years). There apparently is, therefore, a tendency for the Guamanian population to be spared from the development of senile plaques—a tendency that is found not only in the controls but in cases of parkinsonian dementia as well.

As has been brought out, Tomlinson *et al.* (1970) and Dayan (1970*b*) have shown that the presence of severe widespread cortical neurofibrillary degeneration correlates well with dementia, which was documented by psychological testing by Tomlinson *et al.* The question then arises as to whether adequate testing might disclose intellectual impairment in a significant number of our control cases as well.

Elizan, Hirano, Abrams, Need, Van Nuis and Kurland (1966) reported that, in 29 per cent of the cases of parkinsonian dementia, dementia was the only feature of the disease for a variable period of time. In such cases the neuropathological examination would be expected to demonstrate widespread neurofibrillary degeneration without cell loss in the substantia nigra, as seen in a number of our severely affected 'control' cases. It would also be expected that a few of these cases will show some degree of loss in the substantia nigra, thus representing parkinsonism in a subclinical stage.

The available brain weights of the severely affected controls suggest that despite the presence of extensive decrease of neurons as shown by microscopic analysis, the process has not resulted in as marked a degree of atrophy as in the cases of fully developed parkinsonian dementia. The importance of brain weight is highly uncertain; for instance, Tomlinson *et al.* (1970) found that brain weights were not significantly different between the demented as compared with the non-demented patients, and furthermore, that all their brain weights were within the range for normal adults.

In our small series of Caucasians we found no evidence that long residence on Guam predisposes to developing neurofibrillary degeneration.

Our analysis of the frequency of the neurofibrillary degeneration in different Guamanian groups based on village of birth and village of residence at death and positive family history of amyotrophic lateral sclerosis or parkinsonian dementia is suggestive but not conclusive of a positive relationship between the occurrence of neurofibrillary degeneration in controls and in distribution of parkinsonian dementia.

Parkinsonian dementia occurs in males three times more frequently than in females (Brody and Chen, 1969). Neuropathological findings in this series of 69 control Guamanian brains does not follow a similar sex pattern. No significant correlation between high risk geographical areas and neurofibrillary degeneration was observed. We do establish that neurofibrillary degeneration occurs at a very high rate and at an early age in the Chamorro population and with equal frequency and severity among males and females. The suggestion is that, while the neurofibrillary degeneration occurring at the rate observed on Guam is probably related to the extraordinary incidence of parkinsonian dementia in a subpopulation, the relationship is not a direct one. It appears that an external factor (or factors) precipitates the very rapid brain destruction in the fatal clinical condition. It is possible, however, that only those who had prior neurofibrillary degeneration are susceptible to developing parkinsonian dementia.

SUMMARY

In a neuropathological study of the brains of 69 members of the Guamanian Chamorro population without known evidence of dementia, parkinsonism or amyotrophic lateral sclerosis, the incidence and severity of neurofibrillary degeneration was determined in relation to age at death. It was found that neurofibrillary degeneration is present at an earlier age than has been reported for a comparable population in Japan, and much earlier than reported for two similarly comparable English populations. Our data suggests that neurofibrillary degeneration is the common denominator of the Guam neurological syndromes of parkinsonian dementia, amyotrophic lateral sclerosis and dementia without parkinsonism. This conclusion would imply that the ætiological factor of neurofibrillary degeneration is more widely dispersed in the population than suggested by the cases of parkinsonian dementia and amyotrophic lateral sclerosis alone. Both sexes were equally affected while clinical parkinsonian dementia is three times more frequent among males. The sample data suggests a positive association with the amyotrophic lateral sclerosis-parkinsonian dementia rate in village of birth and residence, and also with family history; the results in the small subsamples are not significant. Senile plaques were found in few control cases in this study, just as there has been a relative absence of senile plaques in cases of parkinsonian dementia. In a small group of Caucasians who had spent many of their adult years on Guam, the frequency of neurofibrillary degeneration in relationship to age was comparable to that in the English populations.

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REFERENCES

BRODY, J. A. and CHEN, K. (1969) Changing epidemiologic patterns of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam. In: *Motor Neuron Diseases*. Edited by F. H. Norris and L. T. Kurland. New York: Grune and Stratton, pp. 61-79.

—— HIRANO, A. and SCOTT, R. M. (1971) Recent neuropathologic observations in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. *Neurology, Minneapolis*, **21**, 528-536.

—— STANHOPE, J. M. and KURLAND, L. T. (1975) Patterns of amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. In: *Topics on Tropical Neurology*. Contemporary Neurology Series. Edited by R. W. Hornabrook. Philadelphia: F. A. Davis, pp. 45-70.

CORSELLIS, J. A. N. (1962) *Mental Illness and the Ageing Brain*. London: Oxford University Press.

DAYAN, A. D. (1970*a*) Quantitative histological studies on the aged human brain. I. Senile plaques and neurofibrillary tangles in 'normal' patients. *Acta Neuropathologica, Berlin*, **16**, 85-94.

—— (1970*b*) Quantitative histological studies on the aged human brain. II. Senile plaques and neurofibrillary tangles in senile dementia. *Acta Neuropathologica, Berlin*, **16**, 95-102.

ELIZAN, T. S., HIRANO, A., ABRAMS, B. M., NEED, R. L., VAN NUIS, C. and KURLAND, L. (1966) Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam. *Archives of Neurology, Chicago*, **14**, 356-368.

FORNO, L. S. and ALVORD, E. C. (1971) Pathology of Parkinsonism. I. Some new observations and correlations. In: *Recent Advances in Parkinson's Disease*. Edited by F. H. McDowell and C. H. Markham. Philadelphia: F. A. Davis, pp. 120-130.

GELLERSTEDT, N. (1933) Zur Kenntnis der Hirnveränderungen bei der normalen Altersinvolution. *Upsala läkareförenings förhandlingar*, **38**, 194-408.

HIRANO, A., KURLAND, L. T., KROOTH, R. S. and LESSELL, S. (1961*a*) Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. *Brain*, **84**, 642-661.

—— MALAMUD, N. and KURLAND, L. T. (1961*b*) Parkinsonism-dementia complex, an endemic disease on the island of Guam. II. Pathological features. *Brain*, **84**, 662-679.

—— and ZIMMERMAN, H. M. (1962) Alzheimer's neurofibrillary changes, a topographic study. *Archives of Neurology, Chicago*, **7**, 227-242.

—— MALAMUD, N., ELIZAN, T. S. and KURLAND, L. T. (1966) Amyotrophic lateral sclerosis and parkinsonism-dementia complex on Guam. Further pathological studies. *Archives of Neurology, Chicago*, **15**, 35-51.

KIN, RINSYU (1942) Pathologische Studien uber Greisengehirne. *Fukuoka Acta Medica*, **35**, 1187.

MALAMUD, N. (1965) A comparative study of the neuropathologic findings in senile psychosis and in 'normal' senility. *Journal of the American Geriatric Society, Baltimore*, **13**, 113-117.

MATSUYAMA, H., NAMIKI, H. and WATANABE, I. (1966) Senile changes in the brain in the Japanese. Incidence of Alzheimer's neurofibrillary change and senile plaques. Amsterdam: Excerpta Medica. *International Congress Series*, **100**, 979-980.

NEWTON, R. D. (1948) The identity of Alzheimer's disease and senile dementia and their relationship to senility. *Journal of Mental Science*, **94**, 225.

REED, D. M. and BRODY, J. A. (1975*a*) Amyotrophic lateral sclerosis and parkinsonism-dementia on Guam, 1945–1972. I. Descriptive epidemiology. *American Journal of Epidemiology*, **101,** 287–301.

—— TORRES, J. M. and BRODY, J. A. (1975*b*) Amyotrophic lateral sclerosis and parkinsonism-dementia on Guam, 1945–1972. II. Familial and genetic studies. *American Journal of Epidemiology*, **101,** 302–310.

TOMLINSON, B. E., BLESSED, G. and ROTH, M. (1968) Observations on the brains of non-demented old people. *Journal of Neurological Sciences*, **7,** 331–356.

—— —— —— (1970) Observations on the brains of demented old people. *Journal of Neurological Sciences*, **11,** 205–242.

WILDI, E., LINDER, A. and COSTOULAS, G. (1964) Étude statistique des altérations dégéneratives cérébrales apparaissant au cours du viellissement. *Psychiatria et Neurologia, Basel*, **148,** 41–68.

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Brain (1979), **102**, 79–94

HEREDITARY SENSORY NEUROPATHY WITH SPASTIC PARAPLEGIA

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INTRODUCTION

HICKS (1922) described members of three generations of a large family who developed, usually in the third decade of life, a slowly progressive sensory neuropathy with ulceration of the feet, together with 'lightning' pains and deafness. The pathology of one of Hicks' cases was described by Denny-Brown (1951). He emphasized the loss of posterior root ganglion cells and degeneration of nerve fibres in peripheral nerves and posterior columns of the spinal cord.

Thomas (1975) has classified the hereditary sensory neuropathies into five main groups. The first includes the dominantly-inherited condition described by Hicks, and consists of patients with onset of sensory neuropathy in the second decade of life or later, with the lower limbs predominantly affected and little, if any, involvement of the upper limbs. Progression is usually slow and life expectancy normal.

The second group, 'congenital sensory neuropathy', includes patients reported by Thévenard (1942) and Johnson and Spalding (1964) in whom inheritance is autosomal recessive, the onset is in infancy or early childhood, and both upper and lower limbs are affected. Ulceration and infection of the extremities is generally more severe than in the first group but definite evidence of progression of the neuropathy is lacking.

The third and fourth groups consist of familial dysautonomia (Riley, Day, Greeley and Langford, 1949) and of insensitivity to pain with anhidrosis and mental retardation (Swanson, 1963), and are not relevant to our cases. The fifth group includes the sensory neuropathies associated with the hereditary ataxias.

A small number of cases in the first two groups have shown pyramidal signs in addition to the sensory neuropathy but these have generally been mild; brisk reflexes, extensor plantar responses or, exceptionally, mild spastic weakness. Such signs have been overshadowed by the much more striking mutilating acropathy (van Epps and Kerr, 1940; Spillane and Wells, 1969). However, in the cases described by Jequier, Michail and Streiff (1945) and Khalifeh and Zellweger (1963), spastic paraparesis was the first and significant abnormality and only later did there appear symptoms and signs of a peripheral sensory neuropathy. We have been unable to discover reports of full pathological examination in any of the above cases.

Hereditary spastic paraplegia was first described by Strümpell in 1880 in two brothers whose illness presented in the fourth decade of life. The inheritance has generally been by a dominant mode of transmission, but subsequent reports have been made of cases presenting much earlier in life (Dick and Stevenson, 1953), and these are more frequently recessively inherited (van Bogaert, 1952; Pratt, 1967).

We report five cases of spastic paraplegia with a hereditary sensory neuropathy presenting in early childhood. The sensory neuropathy does not conform well to any of the groups in Thomas' (1975) classification, and the pyramidal involvement is more severe than that generally seen in association with a hereditary sensory neuropathy. Post-mortem findings are reported in one case, and the results of a sural nerve biopsy in another.

CASE REPORTS

Case 1 (*Hospital for Sick Children, No. 468142*)

This boy, now aged 6 years, was born at thirty-two weeks gestation with a birth weight of 2·3 kg. There were no neonatal problems, and concern was first felt when he was 5 months old because his legs were stiff. All aspects of his development have been delayed; he sat unsupported at one year and spoke sentences at two years, but has never walked alone nor gained sphincter control. When first examined at 2 years of age he had a spastic paraplegia with hypertonia of the adductor muscles of the thighs and contractures at the hips, knees and ankles. The tendon reflexes in his legs were increased. There was no abnormality in his arms. At 4 years of age bilateral adductor tenotomies were performed. Post-operatively he needed prolonged ventilation. At 4½ years anxiety was expressed because of injuries to his fingers and his mother said that he seemed not to have felt pain for the past two years (fig. 1A).

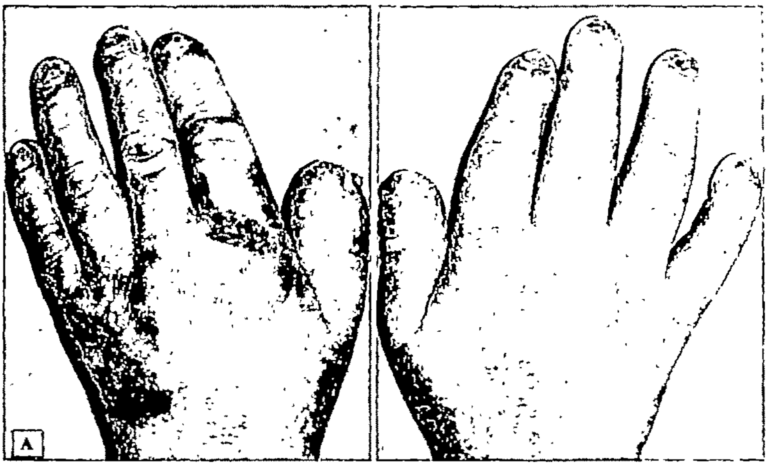
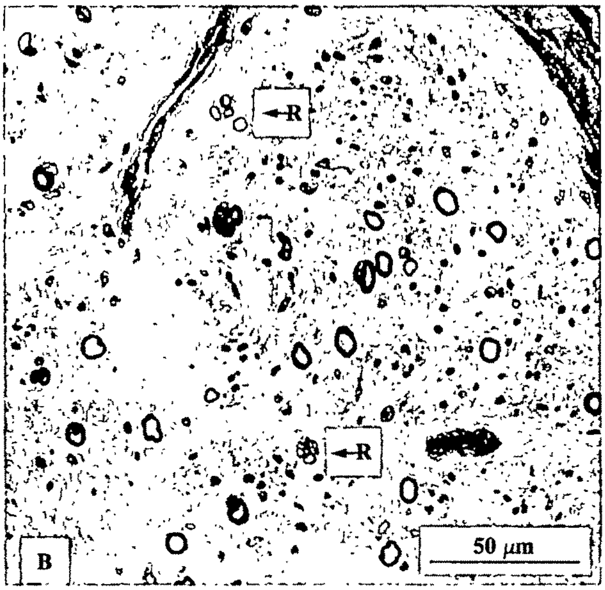
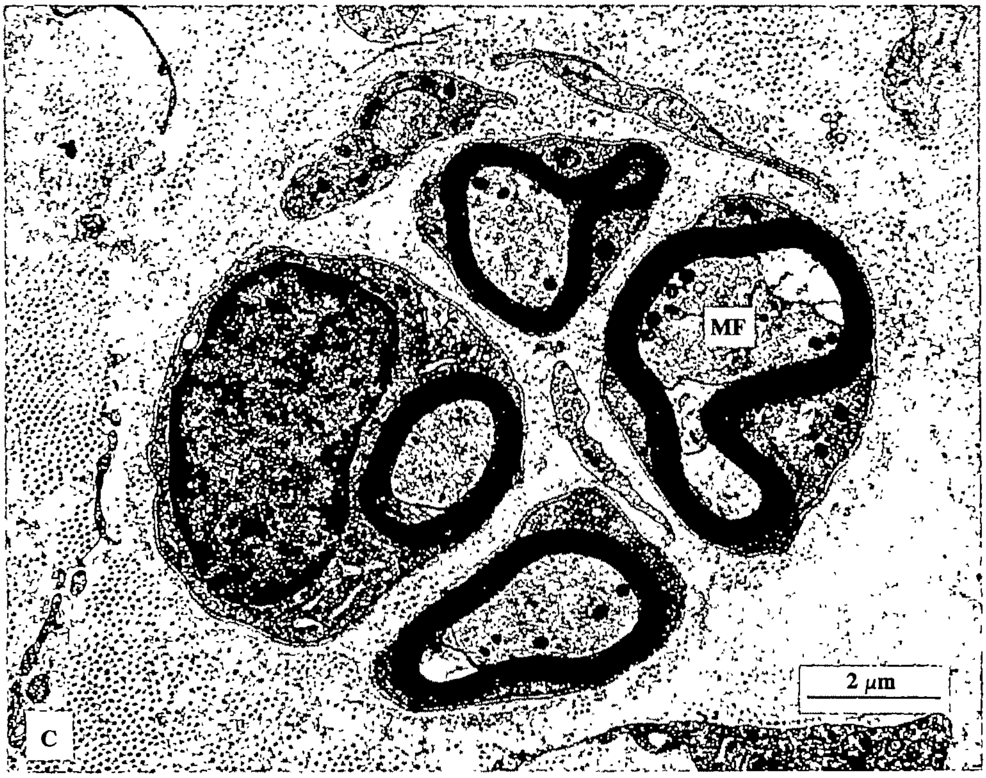


FIG. 1. *Case 1.* A, photograph of both hands. B, light micrograph of sural nerve biopsy showing severe reduction in numbers of myelinated fibres and occasional regenerative clusters (R). Toluidine blue, Epon-embedded. C, electron micrograph, showing a regenerative cluster of small myelinated fibres (MF). Lead hydroxide/uranyl acetate.


R
R
B
50 μm


MF
2 μm
C

Examination showed a boy with a head circumference on 3rd percentile. The cranial nerves were normal. There was hypotonia and weakness of the limbs, more marked in the legs than the arms and more distal than proximal. Co-ordination was normal. All tendon reflexes were reduced and the ankle jerks were absent. Sensory testing showed that appreciation of pain was absent up to the level of the knees and mid-forearms, but that light touch was preserved. Posterior column sensation was difficult to assess. He showed normal sweating and lacrimation.

Investigations. The amino acid pattern in blood and urine was normal. Tests of liver function, electrolytes, urea, blood lactate, copper and zinc, phytanic acid gave normal results. His urine contained no porphyrins or metachromatic material. No acanthocytes were seen in blood films. His blood cholinesterase was in the homozygous range. Electrocardiogram and electroretinogram were normal. Nerve conduction studies showed a prolonged terminal latency and reduced amplitude of motor action potential in the peroneal nerve, but conduction velocity was normal. His IQ was in the low normal range (Stanford Binet). X-rays of the skull showed a thick vault but no other abnormality. A sural nerve biopsy performed when he was 5 years of age showed profound loss of myelinated fibre (fig. 1B) with little evidence of regeneration in the presence of occasional 'regenerative clusters' (fig. 1C), and small newly remyelinated fibres. There was an increase in numbers of Schwann nuclei. Electron microscopy showed that unmyelinated fibres were so few that density estimates were unnecessary. The perineurium and blood vessels were normal. No amyloid material was present.

Case 2 (Hospital for Sick Children, No. 489550)

This 3½-year-old boy is said to be the half-brother to Case 1 by a different father. The pregnancy was complicated by vaginal bleeding, intermittent loss of amniotic fluid and toxæmia. He was delivered at term by vacuum extraction with a birth weight of 2·8 kg. In the newborn period, he had severe respiratory distress and was treated with oxygen. He was hypotonic in the first few weeks of life. He smiled at 8 weeks of age, sat without support at 6 months, crawled at 10 months and soon afterwards was able to walk with support, but cannot yet walk alone. Before the age of one year, his mother already suspected a similar illness to that of his brother. When examined at 14 months of age, he was found to have a spastic paraplegia, with exaggerated reflexes in the legs. His cranial nerves and arms were normal.

At 2½ years it was realised that he was sustaining injury to his hands and feet without feeling pain. At 3 years, his legs were found to be less spastic than before although hypertonia of thigh adductors was still present. The ankle reflexes were now found to be depressed, though the knee jerks were still brisk. The plantar responses were extensor. Appreciation of pain was absent below the level of the knees and mid-forearms. Other forms of sensation could not be reliably assessed. He developed osteomyelitis of the terminal phalanx of his left index finger. At 3½ years of age he still has no control of his sphincters.

Investigations. Normal results were obtained from the same investigations as were performed on his brother. Skull x-rays were normal. The blood cholinesterase level was normal.

Clinically, the boys' mother showed no abnormality on neurological examination. Motor nerve conduction velocities and sensory nerve action potentials were normal.

Case 3 (St. Mary's Hospital, No. 698099)

This patient was unrelated to the previous two. He was the only child of healthy unrelated parents with no family history of neurological disease and was born normally after an uneventful pregnancy. Until the age of 18 months his developmental milestones were normal, but he showed a palmar grasp and tended to drop objects. He walked alone at 2 years of age with a gait described as 'stiff' and falling often. He ran with difficulty. He showed no concern when he bruised or grazed himself, and for the next few years he had frequent sores and blisters on his fingers, which seemed to be painless. He developed a habit of nail-biting and would at times bite his nails off completely. At 6 years of age he lost the terminal phalanx of his right index finger through osteomyelitis. At the same age, he fell out of a tree and sustained a right Pott's fracture. For a week after this, he walked on the fractured leg without discomfort until discovery of the fracture led to referral and neurological assessment. A mild spastic paraparesis and peripheral sensory loss were found and thought to indicate syringomyelia.

Over the next few years he had recurrent ulceration and infection of the hands and feet causing the loss of all the distal phalanges of his fingers and many of those of his toes (fig. 2). Up to the age of 17 years he had nocturnal enuresis and was hardly ever aware of a full bladder.

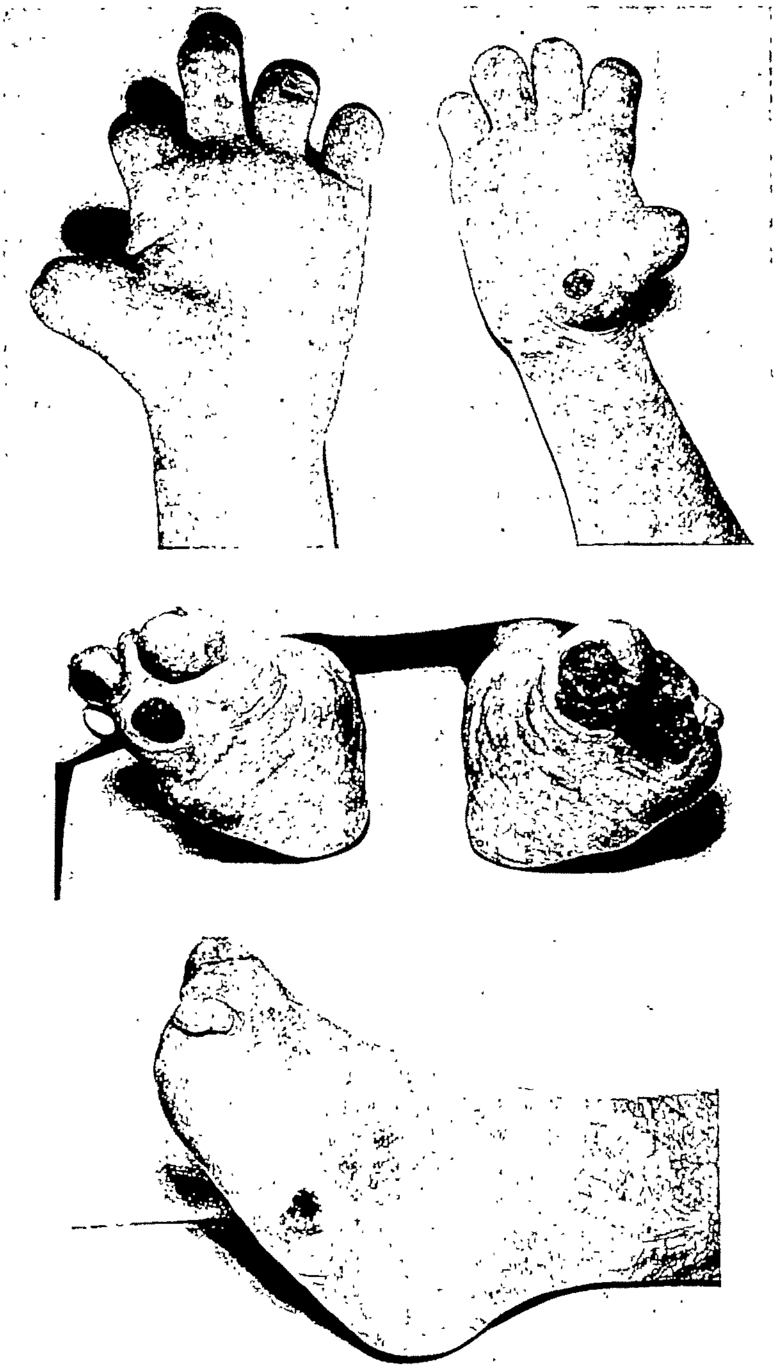


FIG. 2. *Case 3.* Photographs of both hands and feet, aged 16 years.

At the age of 9 years he had the first of many episodes of painless urinary retention which required catheterization. Until he was 15 years of age he had poor control of defæcation with urgency. Neurological examination at 9 years of age showed signs of a symmetrical distal sensory neuropathy (fig. 3A) with absent supinator, triceps and ankle reflexes. He had mild spasticity of both legs with little weakness. Cranial nerves were normal. He had many further episodes of osteomyelitis over the next few years requiring repeated sequestrectomy, and removal of part of his left forefoot at 16 years of age. He habitually walked on his knees in an attempt to avoid ulceration of his feet, and the pattern of his life until his death at 29 years was one of a few days of mobility alternating with months of bed-rest and operations to achieve healing of the resultant ulcers and infections. He became a permanent carrier of resistant strains of Staphylococcus aureus and Pseudomonas pyocyanea. In later years, he often developed ulcers spontaneously.

Examination at the age of 22 years showed normal cranial nerves. The motor system was normal apart from a mild increase in tone in the legs with slight weakness of hip flexion and generalized areflexia. Sensory testing showed a glove and stocking loss to all modalities with a much more extensive impairment of pain and temperature sense over most of the trunk (fig. 3B). Abdominal reflexes were absent. Peripheral nerves were not palpably thickened. Tests for sweating and piloerection gave normal results.

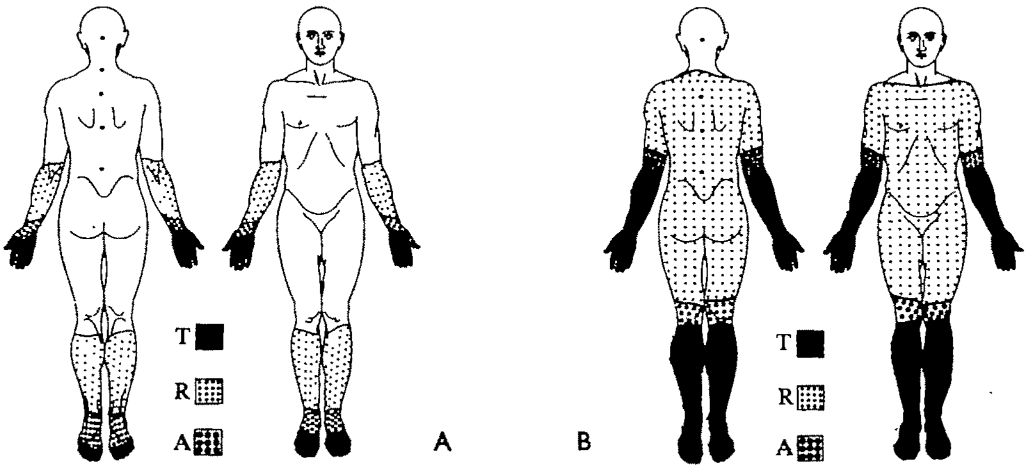


FIG. 3. *Case 3.* A, chart showing distribution of sensory loss at aged 9 years. B, chart at aged 22 years. T = total sensory loss. R = reduced pain and temperature sensation. A = absent pain and temperature sensation.

Investigations. Tests of liver function, electrolytes, urea, full blood picture, blood sugar, pyruvate and glucose tolerance, B_{12} and folate were normal. The cerebrospinal fluid and chromosome analysis were normal. A Congo red test and rectal biopsy were normal. X-ray showed changes typical of neuropathic arthropathy at the ankles and chronic osteomyelitis in both feet. An intravenous pyelogram and micturating cystography were normal. Cardiovascular responses to tilt and Valsalva's manœuvre were normal. Motor conduction velocities of ulnar, median and peroneal nerves and electromyography of a wide range of muscles were all normal. Sensory nerve action potentials were absent from median and ulnar nerves in the forearm. His IQ was 128 (Wechsler). His electroencephalogram (EEG) was normal.

At the age of 27 years he developed a severe nephrotic syndrome and a repeat rectal biopsy showed the presence of amyloid. A progressive deterioration in renal function led to his death two years later.

Post-mortem findings. Macroscopically, the main changes were small bilateral pleural effusions, hepatic congestion and bilateral small pale kidneys. The external appearances of the brain and spinal cord, and of the meninges were entirely normal. The brain weighed 1390 g.

Histological Findings

Kidneys. These showed considerable loss of glomeruli with abundant amyloid material in the remaining glomeruli, renal tubules and small arteries.

Other organs. Amyloid was present in large amounts in the adrenal cortex and in the small arteries of the small intestine and colon. No amyloid was found in liver or spleen.

Central nervous system. The *brain* was examined after formalin fixation, and sections taken from many areas of cortex, white matter and central grey matter showed no significant abnormality.

The spinal cord. Specimens from C2, C7, T3, T7 and L1 were embedded and stained with hæmatoxylin and eosin, cresyl violet, Weigert's stain for myelin, Glees' silver method for axons, Mallory's phosphotungstic acid hæmatoxylin and Holzer's crystal violet. Frozen sections from C6 and T11 were stained with Sudan Black B and Marchi's method for degenerating myelin.

The outline of the cord was preserved. The leptomeninges and blood vessels were within normal limits. The central canal and anterior horns of grey matter were normal. In the posterior columns, loss of fibres with gliosis in the fasciculus cuneatus was marked at all levels examined. In the fasciculus gracilis there was some relative preservation of fibres in the anterior parts in the cervical and thoracic cord (fig. 4). The sensory nuclei of Clarke's column were normal.

There appeared to be no loss of myelinated fibres in the lateral or anterior columns, and Sudan Black and Marchi stains did not demonstrate any evidence of myelin degeneration.

Peripheral nervous system. Posterior root ganglia and roots. There was approximately 50 per cent neuronal loss. Many residual nodules of Nageotte were seen (fig. 5A) together with whorls of argyrophilic fibres resembling proliferated dendrites (fig. 5B). There was striking loss of axons and spheroidal swellings were seen on the remaining axons. The amount of connective tissue was slightly increased. No amyloid material was found.

Peripheral nerves. Specimens of right and left median, ulnar and peroneal nerves were studied. In all, there was extensive loss of myelinated fibres and axons (fig. 5C).

There was no increase in the number of Schwann cell nuclei, and no perineurial thickening or onion-bulb formation. Blood vessels were normal and amyloid was not present.

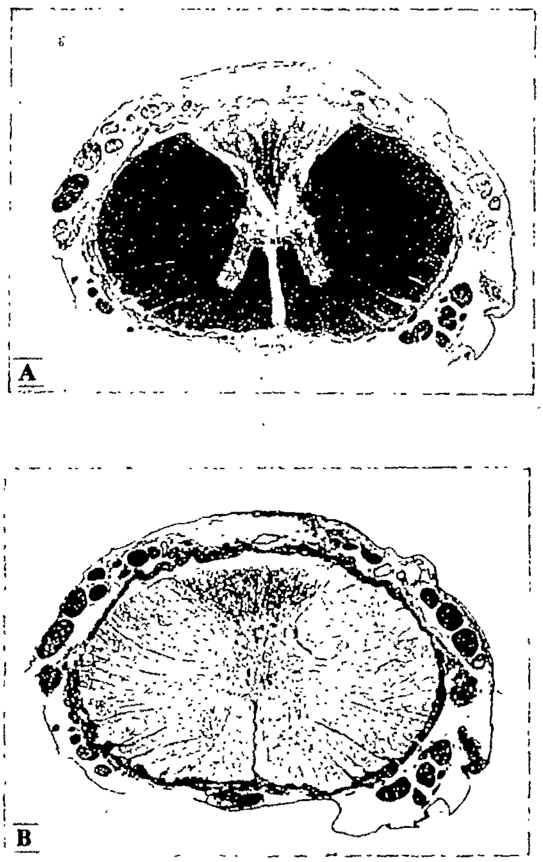


FIG. 4. *Case 3*. Light micrographs of spinal cord showing A, posterior column myelin loss, and B, gliosis. A, Heidenhain's myelin, B, Holzer.

Case 4 (*Maida Vale Hospital, No. 85116*)

This 20-year-old girl was the eldest of six siblings, her affected 16-year-old brother being the third in the sibship. There was no other history of neurological disease. The parents of the patients were first cousins.

Her delivery and early development were normal but at the age of 3½ years her gait was noticed to be abnormal, particularly when she tried to run. At the age of 8 years, the skin over her right big toe became thick, it then ulcerated and she developed osteomyelitis. Soon afterwards her left hallux was affected in the same way. Over the following years she had repeated ulceration and infection of her toes with ten operations for ulceration and removal of sequestra. Pain was never a prominent feature of her illness and she continued to walk without distress. At the age of 16 years, she noticed a slight numbness of her fingers, and the skin over the fingertips became roughened and hard. There was no disturbance of sphincter control.

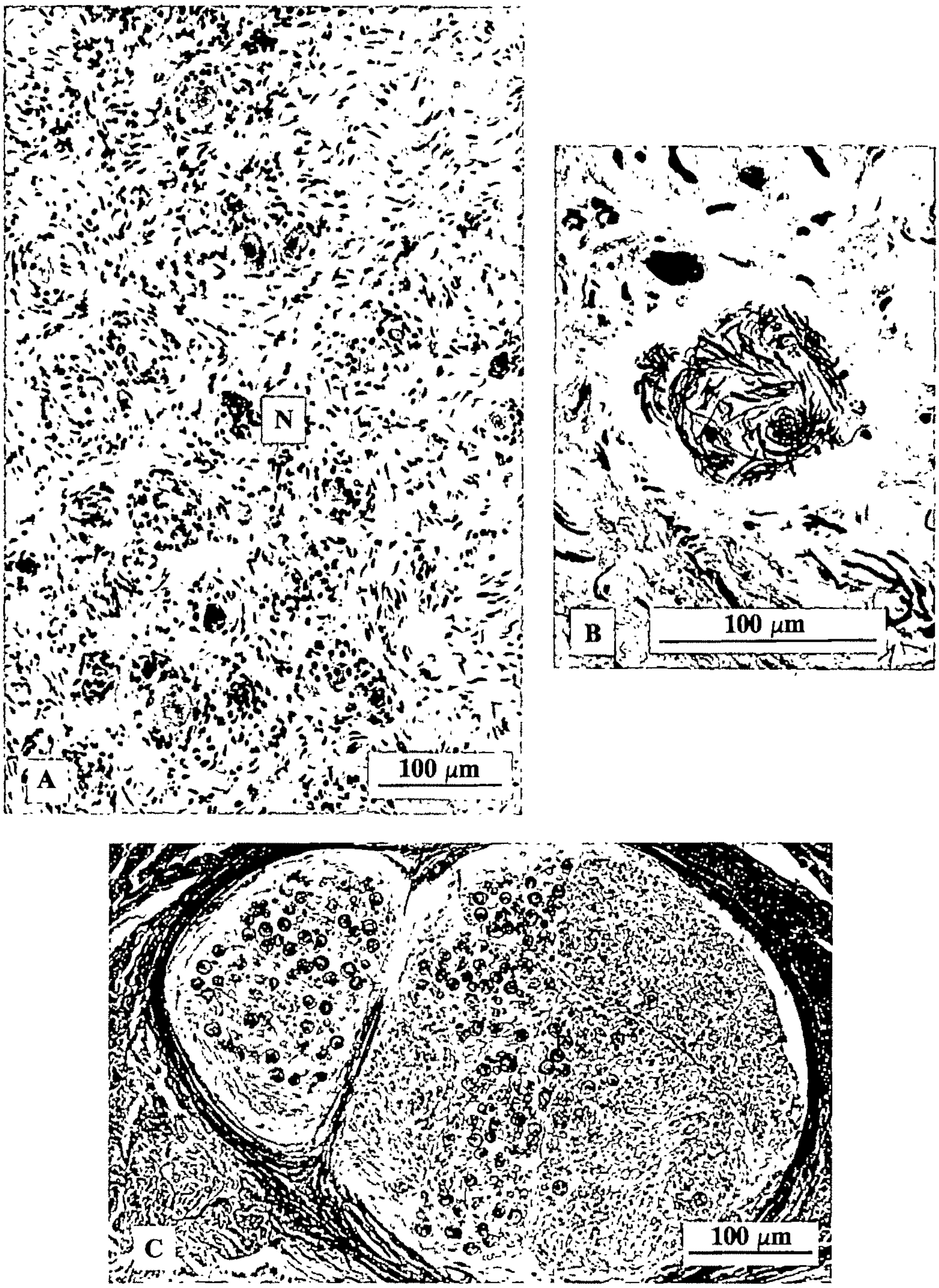


FIG. 5. *Case 3.* A, posterior root ganglion showing reduced number of ganglion cells and residual nodules (N). Hæmatoxylin and eosin. B, posterior root ganglion showing a whorl of argyrophilic fibres. Bielshowsky's silver. C, median nerve showing loss of myelinated fibres. Kulschitsky.

Examination at the age of 20 years showed a fit-looking girl with a spastic gait. She had a long gentle thoracic scoliosis, convex to the right. There were minor trophic changes in her fingers (fig. 6A), and she had an extensive foul-smelling ulcer on the sole of her left foot with considerable deformity (fig. 6B). There was no abnormality of tone, power or reflexes in the arms. Both legs were spastic and there was moderate weakness of hip flexion and foot eversion. The knee jerks were exaggerated and the ankle jerks absent; the plantar responses were extensor. Sensory testing showed an impaired perception of light touch, pain and temperature in a glove and stocking distribution with more extensive involvement of spinothalamic modalities (fig. 7). Vibration and joint position sense were mildly impaired in the feet. She showed no cerebellar deficit.

Investigation. The ESR was 64 mm/h. CSF protein and syphilis serology were normal. X-rays of the feet showed extensive destructive changes in the phalanges and metacarpal bones. X-rays of the spine were normal. A myodil myelogram screened prone and supine throughout showed that the spinal canal was normal.

Case 5 (Maida Vale Hospital, No. 85115)

This boy, the brother of Case 4, was noticed to have an abnormal gait at the age of 4 years, often falling when he tried to run. The skin over his toes and the soles of his feet became thick like that of his sister. From the age of 12 years he had recurrent painless ulceration of the feet and this required several operations. His gait remained abnormal but showed little change over the years. He had occasional flexor spasms. There were no symptoms affecting his upper limbs or sphincters.

Examination at the age of 16 years showed trophic changes limited to the feet, where they were similar to those of his sister. There was an extensive perforating ulcer on the sole of his right foot. His cranial nerves were normal. There was no abnormality of tone or reflexes in his arms. The legs were spastic with mild weakness of pyramidal distribution, most marked distally. Tendon reflexes at the knees were exaggerated and those at the ankles were depressed. The plantar responses were extensor. Sensory testing showed a glove and stocking loss which, as in his sister, was more severe for spinothalamic modalities. Proprioception was preserved. He had a spastic gait; there was no cerebellar deficit.

Investigation. The CSF was normal; x-rays of the lumbar spine and myelography, screened prone and supine, were also normal.

DISCUSSION

The five cases showed the features of a spastic paraplegia present from early childhood, together with a progressive ulcerating distal sensory neuropathy affecting upper as well as lower limbs. Spinal cord compression and syringomyelia have been excluded as causes of the paraplegia which, with the neuropathy, is believed to be inherited. Recurrent infections of the injured limbs lead to the early development of osteomyelitis. Of all sensory modalities, pain and temperature are the most severely affected. Intelligence is unaffected, and there are no cranial nerve abnormalities.

Within the 5 cases, there are differences mainly in the age of onset and the rate of progression of the disorder. In the first 3 cases, the paraplegia developed within the first two years of life and was associated at an early stage with the clinical features of a peripheral neuropathy. By contrast in Cases 4 and 5 both the paraplegia and neuropathy became evident much later, though difficult to date precisely.

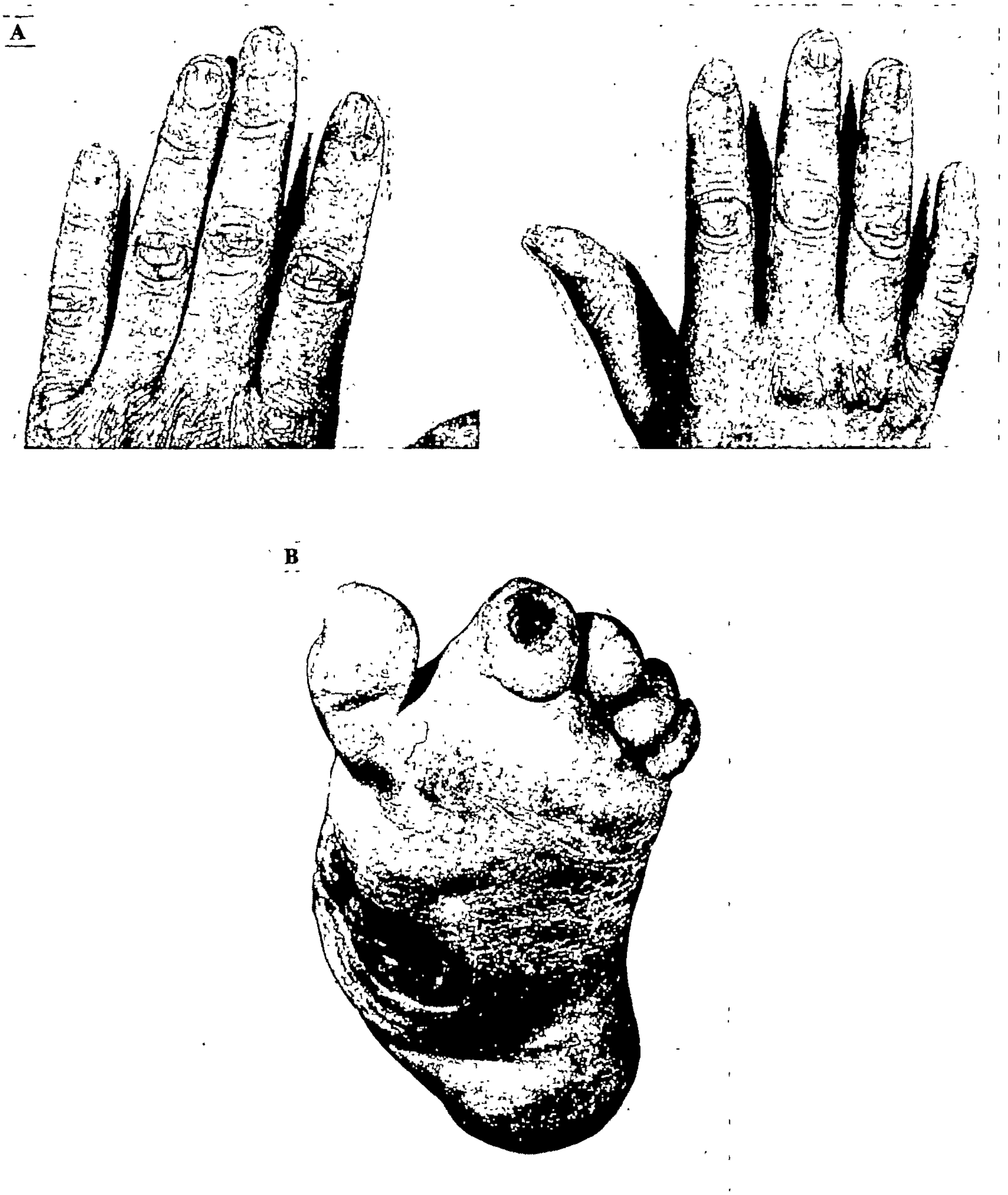


FIG. 6. *Case 4*. A, early trophic changes in fingers. B, perforating ulcer, left foot.

Over the period of observation, neither Case 1 nor Case 2 had gained bowel or bladder control, and Case 3 had recurrent urinary retention and fæcal urgency, whereas there had been no sphincter disturbances in Cases 4 and 5.

If an attempt is to be made to classify our patients, on the basis of their sensory neuropathy, it is clear that they do not correspond to any of Thomas' (1975) groups. The equal involvement of lower and upper extremities in the first 3 cases together with the early onset in all cases, would favour his second group, but the clear evidence of progression shown by the increasingly severe sensory impairment and the gradual loss of tendon reflexes are against this classification. The greater impairment of temperature and pain sensation is also unlike that usually found in his second group of cases.

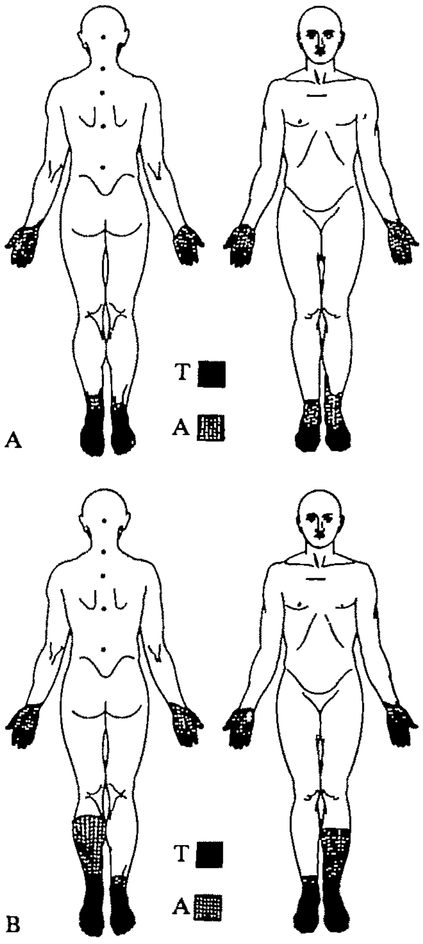


FIG. 7. *Cases 4* (A) and *5* (B). Charts showing distribution of sensory loss. T = total sensory loss. A = absent pain and temperature sensation.

The question of inheritance in our patients is difficult. Four are boys and there are 2 pairs of siblings. Cases 1 and 2 may be half-brothers by the same mother but of uncertain paternity. It proved impossible to investigate their paternity further; it may be that the father is the same in each case, or that their two fathers are related to each other or to the mother. There is no relevant family history in Case 3; Cases 4 and 5 are brother and sister with normal, but consanguineous, parents and several other normal siblings. The inheritance is therefore probably by an autosomal recessive mechanism, but in view of the range of clinical features seen within the groups of cases, genetic heterogeneity cannot be excluded.

Hereditary sensory neuropathy has been found in association with other defects and disorders, such as deafness (Hicks, 1922); motor neuropathy and peroneal muscular atrophy (England and Denny-Brown, 1952; Wadia and Dastur, 1960; Spillane and Wells, 1969); mental retardation (Ogden, Robert and Carmichael, 1959); Friedreich's ataxia (Bugiani and van Bogaert, 1967); and with a combination of hare lip, cleft palate and meningocœle (Reimann, McKechnie and Stanisavljevic, 1958). In addition, pathological evidence of cerebellar and inferior olivary involvement was found in a case similar to those described by Hicks (Blackwood, 1952).

Hereditary spastic paraplegia has also been reported in association with other disorders, particularly motor neuropathy and peroneal muscular atrophy (Silver, 1966; Cross and McKusick, 1967). Despite the pathological evidence of posterior column involvement in some cases (Roe, 1963) there is usually little or no sensory disability. Many families reported have suffered from a progressive form of the disorder, but none of our patients have shown any increase with time in their pyramidal symptoms or signs.

It is clear that our patients suffer from a progressive sensory disorder which at its most severe carries a very poor prognosis; in such cases life is threatened by recurrent osteomyelitis and secondary amyloidosis. Even with the most active and intelligent measures, these infections cannot be avoided.

Apart from the conditions mentioned in the Introduction within Thomas' (1975) classification, the differential diagnosis of a mutilating sensory neuropathy in childhood should include syringomyelia, 'congenital indifference to pain' (Dearborn, 1932), leprosy, and the Lesch-Nyhan syndrome. The clinical picture in all cases was unlike that of syringomyelia which was excluded by myelography in Cases 4 and 5 and on pathological grounds in Case 3. The syndrome of 'congenital indifference to pain' is not associated with a peripheral neuropathy. The age of onset and the pathology exclude leprosy as a cause of the ulceration. The Lesch-Nyhan syndrome is X-linked and includes athetoid movements which were absent in our cases.

The absence of abnormality on muscle sampling or slowing of motor nerve conduction velocity excludes peroneal muscular atrophy. The spinocerebellar ataxias can be excluded on both clinical and pathological grounds.

In the sural nerve biopsy from Case 1, there is evidence of myelinated fibre degeneration and regeneration as shown by the presence of myelin debris and regenerative 'clusters'. In the cases of congenital sensory neuropathy described by Murray (1973), and of hereditary sensory neuropathy described by Schoene, Asbury, Åström and Masters (1970) there was profound absence of myelinated fibres with little or no evidence of degeneration and regeneration. Murray (1973) suggested that in his cases, which were clinically non-progressive, there was either congenital absence of peripheral sensory fibres or that degeneration had taken place during early development. However, in the cases of congenital sensory neuropathy described by Ohta, Ellefson, Lambert and Dyck (1973) biopsy showed evidence of myelinated fibre degeneration and some regenerative activity. Schoene, *et al.* (1970) and Dyck (1975) have stressed the point that in very slowly progressive chronic neuropathy evidence of nerve fibre degeneration is usually lacking, but it seems possible that where there is clinical evidence of more rapid progression, features indicating nerve fibre degeneration and regeneration may be found on nerve biopsy.

The pathological findings in Denny-Brown's original case were very similar to the findings in our Case 3, particularly the appearances of posterior root ganglia. These show marked loss of ganglion cells, and their replacement not only by residual nodules of satellite cells but also by whorls of thickened argyrophilic fibres resembling abnormal and sprouting axons. Denny-Brown found amyloid deposits in the ganglia in his case, although there was no other evidence of amyloidosis, and he questioned whether this was an isolated finding or whether it was an early indication of secondary amyloidosis. In our Case 3, however, the presence of massive amounts of amyloid in kidneys, intestines and adrenal medulla confirms the diagnosis of secondary amyloidosis, in which amyloid is usually absent in both the peripheral and central nervous systems. The clear history of severe recurrent osteomyelitis with initially negative and later positive tests for amyloid, as well as the pathological distribution, excludes amyloid as a primary cause of the neuropathy.

The marked loss of myelinated fibres in the posterior columns contrasts with the normal appearance of the rest of the spinal cord and central nervous system; in particular, no abnormality in the lateral columns could be found to account for the early paraparesis. It is possible that such changes were too mild to be recognized. Post-mortem reports on previous cases of hereditary spastic paraplegia have shown predominent loss of myelinated fibres in the lateral and anterior columns of the spinal cord; a reduction in number of Betz cells in the cerebral cortex has also been reported (Schwartz and Liu, 1956). Such reports, however, were made on cases with severe progressive paraplegia, and our Case 3 has a mild paraplegia and had shown no evidence of progression. Examination of the spinal cord in a more severely affected case might be expected to show pathological changes.

The question must be raised whether the fundamental pathological disorder in these cases is neuronal atrophy. The term 'hereditary sensory radicular neuropathy' used by Denny-Brown implies a defect of the posterior root ganglion, producing degeneration of both peripheral and central fibres. This may well be true in our patients and the increasing sensory loss is consistent with the 'dying back' type of fibre degeneration found in cases of neuronal atrophy. The association of sensory neuropathy with spastic paraparesis may indicate a disorder involving both posterior root ganglion cells and pyramidal tract neurons but we have no pathological evidence of involvement of the latter.

SUMMARY

Five cases of spastic paraplegia with a progressive symmetrical sensory neuropathy producing ulceration and osteomyelitis of the hands and feet are reported. The pathology in one patient, who died of secondary amyloidosis, was similar to that found by Denny-Brown in hereditary sensory radicular neuropathy with severe loss of posterior root ganglion cells and loss of myelinated fibres in both peripheral nerves and posterior columns of the spinal cord. A sural nerve biopsy in another case showed a striking loss of both myelinated and unmyelinated fibres, with some evidence of degeneration and regeneration. The inheritance is probably by an autosomal recessive gene. The prognosis in the more severe form of the disorder is poor.

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REFERENCES

BLACKWOOD, W. (1952) Biopsy technique in the diagnosis of peripheral neuropathies (especially hereditary and sensory neuropathy). In: *Proceedings of the 1st International Congress of Neuropathology (Rome)*. Amsterdam: Excerpta Medica, Vol. 3, pp. 415–424.

BOGAERT, L. VAN (1952) Étude génétique sur les paraplégies spasmodiques familiales. *Journal de Génétique Humaine*, **1**, 6–23.

BUGIANI, O. and BOGAERT, L. VAN (1967) Sur la transformation dans le temps des phénotypes abiotrophiques. D'une hérédoataxie á l'acropathie ulcéromutilante. *Psychiatria, Neurologia, Neurochirurgia Amsterdam*, **70**, 281–304.

CROSS, H. E. and MCKUSICK, V. A. (1967) The Troyer syndrome. A recessive form of spastic paraplegia with distal muscle wasting. *Archives of Neurology, Chicago*, **16**, 473–485.

DEARBORN, G. V. (1932) A case of congenital general pure analgesia. *Journal of Nervous and Mental Disease*, **75**, 612–615.

DENNY-BROWN, D. (1951) Hereditary sensory radicular neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 237–252.

DICK, A. P. and STEVENSON, C. J. (1953) Hereditary spastic paraplegia; report of family with associated extrapyramidal signs. *Lancet*, **i**, 921–923.

DYCK, P. J. (1975) In: *Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas and E. H. Lambert. New York: W. B. Saunders Co., Vol. II, Chapter 40, pp. 791-824.

ENGLAND, A. C. and DENNY-BROWN, D. (1952) Severe sensory changes, and trophic disorder, in peroneal muscular atrophy (Charcot-Marie-Tooth type). *AMA Archives of Neurology and Psychiatry*, **67**, 1-22.

EPPS, C. VAN and KERR, H. D. (1940) Familial lumbosacral syringomyelia. *Radiology*, **35**, 160-173.

HICKS, E. P. (1922) Hereditary perforating ulcer of the foot. *Lancet*, **i**, 319-321.

JEQUIER, M., MICHAIL, J. and STREIFF, E. B. (1945) Paraplégie familiale et dégénérescence tapéto-rétinienne. *Confinia Neurologica*, **6**, 277-280.

JOHNSON, R. H. and SPALDING, J. M. K. (1964) Progressive sensory neuropathy in children. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 125-130.

KHALIFEH, R. R. and ZELLWEGER, H. (1963) Hereditary sensory neuropathy with spinal cord disease. *Neurology, Minneapolis*, **13**, 405-411.

MURRAY, T. J. (1973) Congenital sensory neuropathy. *Brain*, **96**, 387-394.

OGDEN, T. E., ROBERT, F. and CARMICHAEL, E. A. (1959) Some sensory syndromes in children; indifference to pain and sensory neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **22**, 267-276.

OHTA, M., ELLEFSON, R. D., LAMBERT, E. H. and DYCK, P. J. (1973) Hereditary sensory neuropathy, Type II. *Archives of Neurology, Chicago*, **29**, 23-37.

PRATT, R. T. C. (1967) *The Genetics of Neurological Disorders*. London: Oxford University Press, pp. 44-48.

REIMANN, H. A., MCKECHNIE, W. G. and STANISAVLJEVIC, S. (1958) Hereditary sensory neuropathy and other defects in a large family. *American Journal of Medicine*, **25**, 573-579.

RILEY, C. M., DAY, R. L., GREELEY, D. MCL. and LANGFORD, W. S. (1949) Central autonomic dysfunction with defective lacrimation: report of 5 cases. *Paediatrics*, **3**, 468-478.

ROE, P. F. (1963) Hereditary spastic paraplegia. *Journal of Neurology, Neurosurgery and Psychiatry*, **26**, 516-519.

SCHOENE, W. C., ASBURY, A. K., ÅSTRÖM, K. E. and MASTERS, R. (1970) Hereditary sensory neuropathy. A clinical and ultrastructural study. *Journal of the Neurological Sciences*, **11**, 463-487.

SCHWARTZ, G. A. and LIU, C.-N. (1956) Hereditary (familial) spastic paraplegia. *AMA Archives of Neurology and Psychiatry*, **75**, 144-162.

SILVER, J. R. (1966) Familial spastic paraplegia with amyotrophy of the hands. *Journal of Neurology, Neurosurgery and Psychiatry*, **29**, 135-144.

SPILLANE, J. D. and WELLS, C. E. C. (1969) *Acrodystrophic Neuropathy*. London: Oxford University Press.

STRÜMPELL, A. (1880) Beiträge zur Pathologie des Ruckenmarks. *Archiv für Psychiatrie und Nervenkrankheiten*, **10**, 676-717.

SWANSON, A. G. (1963) Congenital insensitivity to pain with anhydrosis. *Archives of Neurology, Chicago*, **8**, 299-306.

THÉVENARD, A. (1942) L'acropathie ulcéro-mutilante familiale. *Revue Neurologique*, **74**, 193-212.

THOMAS, P. K. (1975) In: *Recent Advances in Clinical Neurology, No. 1*. Edited by W. B. Matthews. Edinburgh: Churchill Livingstone, pp. 253-283.

WADIA, N. H. and DASTUR, D. K. (1960) Congenital sensory neuropathy. *World Neurology*, **1**, 409-421.

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Brain (1979), **102**, 95–125

DORSAL COLUMN NUCLEI AND ASCENDING SPINAL AFFERENTS IN MACAQUES

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INTRODUCTION

SINCE the last decade various interpretations of the functional role attributed to the dorsal column-medial lemniscal system (DCMLS) have been proposed mainly on the basis of behavioural observations in experimental monkeys or clinical deficits in patients with spinal cord lesions (Brown and Gordon, 1977; Wall and Noordenbos, 1977). At the same time, only sparse attention has been directed to the structure of the dorsal column nuclei (DCN) and their connections in primates. Following the classical studies with retrograde degeneration and the Marchi method, in few instances have the DCN of monkeys been investigated with modern neuroanatomical methods. Shriver, Stein and Carpenter (1968) and Carpenter, Stein and Shriver (1968), using the Nauta technique, described the distribution of dorsal root fibres from representative levels throughout the cord to the gracile and cuneate nuclei as well as to adjacent medullary nuclei. More recently, labelling of thalamic projecting cells in the DCN of monkeys by the retrograde transport of horseradish peroxidase has been reported in a brief communication by Albe-Fessard, Boivie, Grant and Levante (1975), while the terminal distribution of the axon of such cells has been described in detail by Boivie (1978), who made use of the Fink-Heimer technique primarily.

New questions about the anatomical organization of the dorsal column-medial lemniscal system in primates arise from the observation that in cats the DCN are not homogeneously organized but contain neuronal populations which may be distinguished by their cytoarchitectonic and electrophysiological characteristics (Beck, 1976). Also, evidence in favour of a complex system of afferent and efferent connections of the feline DCN has been accumulated in several laboratories by experiments using degeneration methods and axonal transport techniques (for a review, *see* Hand and van Winkle, 1977). These data demand a less traditional view of the feline DCMLS. At the same time, the question arises whether in primates the organization of this major ascending pathway may also be more complex than is currently believed. Information in this regard is, at present, very limited (Biedenbach, 1972; Rustioni, 1977; Burton and Loewy, 1977).

This report focuses on the terminal distribution, within the DCN complex of *macaques*, of ascending spinal pathways (non-primary afferents) in the dorsal and lateral funiculi as demonstrated by means of anterograde degeneration and axonal transport techniques. Additional evidence, based on the retrograde transport of horseradish peroxidase, is also provided in support of previous preliminary observations (Rustioni, 1977) regarding the identification of cells of origin of non-primary afferents to the DCN in the spinal cord of primates.

MATERIAL AND METHODS

Adult monkeys (*Macaca mulatta* and *Macaca fascicularis*) have been used for the present observations. The medullæ of two unoperated animals, fixed by intra-aortic perfusion with 10 per cent formalin, were embedded in celloidin and cut serially in horizontal or transverse sections 40 μm thick. These were stained according to the Klüver-Barrera technique and used for preparation of the cytoarchitectonic map of the medulla graphically reconstructed in fig. 1.

Identification of nuclear boundaries and of thalamic projecting neurons of the dorsal column nuclei was made possible in two animals (29 and 36) with multiple injections of 30 per cent horseradish peroxidase (HRP, Boeringher grade 1; total of 10 μl per animal) in the right nucleus ventralis posterolateralis. Injections were made using a 10 μl Hamilton syringe mounted on the electrode carrier of a stereotaxic apparatus (A: + 8 through + 4·5; L: 5 through 9; H: + 8 through + 11; Olszewsky, 1952). Forty-eight hours after the injection of HRP the animals were perfused with 0·9 per cent saline followed by a double aldehyde mixture (0·5 per cent paraformaldehyde and 2·5 per cent glutaraldehyde in 0·1 M phosphate buffer at pH 7·2). After perfusion, brain and brain-stem slabs were soaked for at least 24 h in 0·1 M phosphate buffer at pH 7·2 to which sucrose was added at a concentration of 30 per cent. Serial frozen 40 μm thick sections of thalamus and medulla were incubated with Hanker-Yates substrate (Hanker, Yates, Metz and Rustioni, 1977) and subsequently lightly stained with 0·1 per cent cresylecht-violet.

For the investigation of the terminal distribution of non-primary afferents to the DCN, the Fink-Heimer degeneration technique was used in 4 animals (fig. 6). In 2 of these animals (14 and 17), non-primary afferents were interrupted at upper cervical or upper lumbar levels twelve to fourteen months after dorsal root ganglionectomy at cervicothoracic or lumbar levels, respectively. In Case 14, dorsal root ganglia T12 to L6 were extirpated bilaterally, and a transection at L6 was performed to interrupt primary afferents from caudalmost dorsal roots, without impairing sphincteric reflexes. Since axonal debris is no longer visualized with silver techniques one year after a fibre tract lesion (Rustioni, 1973; Hopkins and Lawrence, 1975), degeneration at medullary levels after the second lesion, made at L1–L2 fourteen months after deafferentation, can be ascribed to selective interruption of non-primary afferents arising from spinal segments L2 to L6. In Case 17, the dorsal root ganglionectomy was confined to the left side and included C2 to T4. A lesion aimed at the left dorsal funiculus was performed in this case at C3 twelve months after deafferentation. The actual lesion encroaches upon the dorsal horn and the dorsal part of the lateral funiculus on the same side. This intervention interrupts non-primary afferents from levels below C3 but also primary afferent fibres from below T4. However, since only very few primary afferents from dorsal roots below T4 distribute to the cuneate nucleus (Ferraro and Barrera, 1935*a*; Shriver, Stein and Carpenter, 1968), degeneration induced in this nucleus by the second lesion can be ascribed mainly to interruption of non-primary afferents ascending in the dorsal funiculus and in the dorsal part of the lateral funiculus (Rustioni and Molenaar, 1975). Monkeys 14 and 17 were perfused with 10 per cent formalin seven days after the second lesion. During the period of survival allowed these two monkeys, ethical considerations about the use of chronically deafferented animals were not ignored. Thanks to the excellent boarding facilities and veterinary care available at our institution, in the year or more after deafferentation the animals displayed no physical or behavioural manifestation of prolonged pain or even discomfort. Only occasionally were they observed to bite their extremities; such behaviour was interrupted by painting the animal's extremities with iodide tincture of the type commonly used as a disinfectant. Deafferentation had suppressed all afferent input from the affected limb(s) and thus, presumably, abolished pain transmission. Whether deafferented animals suffer any kind of phantom pain cannot be known; however, no sign of serious distress related to the deafferentation could be discerned in these monkeys.

A lesion in the dorsal part of the lateral funiculus was made in 2 other monkeys (25 at T1 and 34 at C3) to study the distribution pattern of afferents to the DCN ascending in this part of the spinal white matter. Since these monkeys had not been chronically deafferented, the operation was performed with special care to avoid damage to dorsal root fibres and/or dorsal columns; largely for this reason the most dorsal part of the lateral funiculus was spared by the lesion in both animals. These 2 monkeys were also killed by intraortic perfusion with 10 per cent formalin seven days after the lesion. Transverse 20 μm thick frozen sections of the medulla and pertinent spinal segments of all 4 animals were collected in serial groups of ten, and one section out of each group of ten was impregnated according to the Fink-Heimer method.

In 4 additional monkeys, the distribution of non-primary afferents to the DCN was studied with autoradiographic techniques (Cowan, Gottlieb, Hendrickson, Price and Woolsey, 1972). A 1 : 1 mixture of L-Leucine 4,5-^{3}H(N) (New England Nuclear, spec. act. 24·5 Ci/mmol) and L-Proline 2,3-^{3}H(N) (New England Nuclear, spec. act. 24·5 Ci/mmol) was desiccated and diluted to concentrations of 40–50 μCi/μl with distilled water. Multiple injections of the resulting solution were made in either the brachial or the lumbar cord with a CR700-20 Hamilton syringe fitted with a 26S-gauge needle. In 3 of the 4 monkeys the isotope injection was aimed at the dorsal horn where spino-DCN neurons are concentrated (Rustioni, 1977); the remaining animal (31), with more ventrally placed injection, served to investigate whether any significant contribution to non-primary afferents might arise from the intermediate zone and ventral horn of the brachial cord of monkeys (fig. 12). After a survival of four to seven days monkeys were perfused with 10 per cent formalin, and the medulla and spinal cord segments were embedded in paraffin. Blocks were subsequently cut in 10 μm thick sections which were mounted on glass slides, coated with Kodak NTB2 nuclear track emulsion and exposed for six weeks at 4° C. Slides were developed in Kodak D-19 at 18° C for 2 min, fixed in Kodak EXTA-FLO for 6 min and washed in running tap water. Sections were counterstained through the emulsion with 0·25 per cent thionine. Counts of silver grains at selected levels of the medulla were made under dark-field illumination with the aid of an interactive graphics system under computer control. Background levels of radioactivity were gauged in sections from which quantitative data were derived by automated counts of grains in the emulsion overlying the hypoglossal nucleus.

Cells of origin of non-primary afferents have been identified in 8 monkeys. Single or multiple injections of 30 per cent HRP (Sigma Type VI or Boeringher Grade 1) were made in one or both sides of the medulla with a CR700-20 Hamilton syringe fitted with a 26S gauge needle. Total volume injected on one side of the medulla ranged from 0·05 to 1·0 μl. After 48 to 72 h all animals were perfused with 0·9 per cent saline, followed by a double aldehyde mixture (0·5 per cent paraformaldehyde and 2·5 per cent glutaraldehyde in 0·1M phosphate buffer at pH 7·2). After perfusion, brain and spinal cord segments were soaked for at least 24 h in 0·1M phosphate buffer at pH 7·2 to which sucrose was added at a concentration of 30 per cent. Serial frozen 40 μm sections through medulla and spinal cord segments were incubated in 3,3′-diaminobenzidine-tetrahydrochloride in 6 animals (fig. 16) and in the Hanker-Yates substrate in the remaining 2 animals (32 and 35).

RESULTS

Cytoarchitectonics and Thalamic Projections of DCN

As a prerequisite for mapping the distribution of non-primary afferents to the DCN of monkeys, the cytoarchitecture of these nuclei has been studied in normal medullæ stained according to the Klüver-Barrera technique and in the medullæ of animals with HRP injections in the thalamus (figs. 1, 2, and 3).

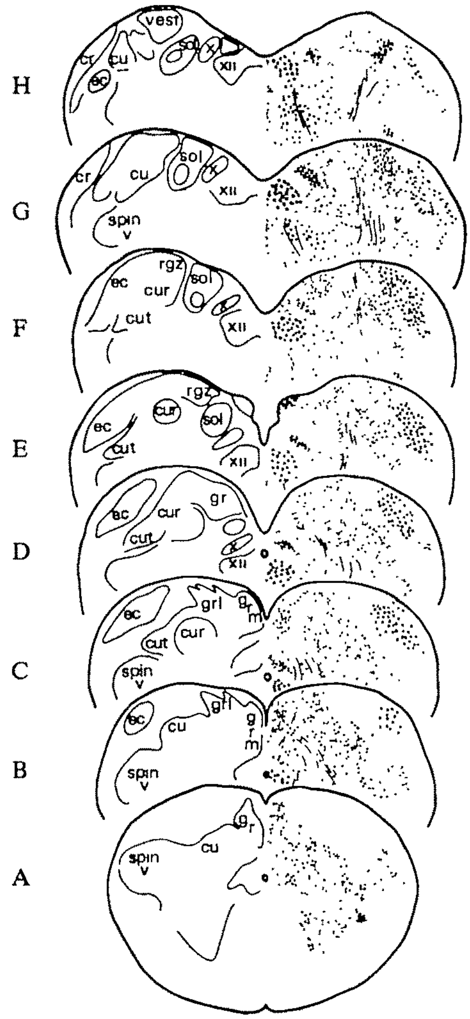

FIG. 1. Nuclear groups in the medulla of macaques are schematically represented in drawings from evenly spaced (640 μm) serial sections, stained according to the Klüver-Barrera technique. Abbreviations for this and the other illustrations: cr: corpus restiforme; cu: cuneate n.; cur: pars rotunda of cuneate n.; cut: pars triangularis of cuneate n.; ec: external cuneate n.; gr: gracile n.; grm: pars medialis of gracile n.; grl: pars lateralis of gracile n.; lrn: lateral reticular n.; rgz: rostral gracile-nucleus Z complex; sol: solitary tract and n.; spin V: spinal nucleus of the trigeminal complex; vest: vestibular complex; x: dorsal motor n. of vagus; xii: hypoglossal n.

The gracile nucleus is only moderately developed at the level of the decussation of the pyramids, and its cytoarchitectonic appearance is relatively homogeneous (fig. 1A). Starting from the level of the caudal pole of the external cuneate nucleus and proceeding rostrally, two regions can be distinguished within the gracile nucleus: a lateral part (grl) in which elongated and fusiform neuronal bodies are arranged in irregular strands which are obliquely orientated, and a medial part (grm) containing multipolar or oval neurons frequently arranged in groups (fig. 1B, C and fig. 3B). The longer diameter of intensely stained perikarya in the lateral part of the gracile nucleus is mainly between 15 and 32 μm. Intensely stained neurons in the medial part have diameters ranging mostly from 14 to 28 μm. Grm and grl are distinguishable throughout about two-thirds of the rostro-caudal extent of the nucleus and closely correspond to pars dorsomedialis and pars ventrolateralis, respectively, as described by Chang and Ruch (1947) in the spider monkey (*Ateles ater*). Similarly, Carpenter, Stein and Shriver (1968) have recognized in the gracile nucleus of rhesus monkeys a medially located core region, receiving dorsal root afferents innervating the distal portion of the hindlimb, and lateral laminæ, to which fibres from thoracic and upper lumbar roots mainly project. Whether in monkeys, as in cats, the rostralmost part of the gracile nucleus should be regarded as a distinct nucleus (nucleus Z) is not settled by the present observations. In agreement with Boivie's (1978) observations, it appears that, if in monkeys there are medullary neurons homologous to the nucleus Z of cats these neurons can hardly be distinguished from gracile neurons. A similar conclusion may be applied with regard to identification of nucleus Z in the human medulla (Sadjadpour and Brodal, 1968).

Observations on the cuneate nucleus of unoperated animals are in agreement with those reported by Ferraro and Barrera (1935*b*). Two portions can be recognized in this nucleus, except at its caudal and rostral poles. The pars rotunda occupies a ventromedial region of the nucleus and appears to be formed mainly by round or oval, intensely staining perikarya, the diameter of which is mainly between 20 and 30 μm (fig. 1C, D, E, F, and fig. 3A). These cells frequently appear grouped in clusters of about 10 to 12 elements per cluster (fig. 3C). The pars rotunda is surrounded by cell bodies of more variable size and shape and more uniform distribution. Neurons of this type are mainly grouped in two triangular regions (pars triangularis) one dorsal to the pars rotunda, the other interposed between pars rotunda and the spinal trigeminal nucleus. At the most rostral levels of the cuneate nucleus (fig. 1F, G) no clearcut separation is visible between this nucleus and the external cuneate nucleus. When the distribution of cervical and upper thoracic dorsal root fibres is taken into account (Shriver, Stein and Carpenter, 1968), pars rotunda forms within the cuneate nucleus a core region containing an expanded representation of distal dermatomes of the upper limb (C6–T1). Fibres from more proximal cervical dermatomes, on the other hand, are mainly represented in the pars triangularis of the same nucleus, while at the rostral and caudal poles of the nucleus, cervical and uppermost thoracic dorsal roots are arranged somatotopically in such a way that each dermatome is represented in slightly overlapping nuclear territories roughly comparable in size.

Numerous small (8 to 12 μm), lightly staining neuronal bodies are present throughout the gracile and cuneate nuclei at all rostro-caudal levels. Exact identification of such elements as interneurons depends on further investigation specifically directed to this goal. Although the size and staining properties of these cells, as revealed in the present Klüver-Barrera material, are similar to those of neurons referred to as interneurons in other brain regions (Rakic, 1975), it should be pointed out that at least some of the neurons within this size range are labelled by HRP injections in the thalamus (*see below*).

Thalamic projecting neurons in the DCN were identified in 2 monkeys with HRP injections in the nucleus ventralis posterolateralis (fig. 2). Distribution and

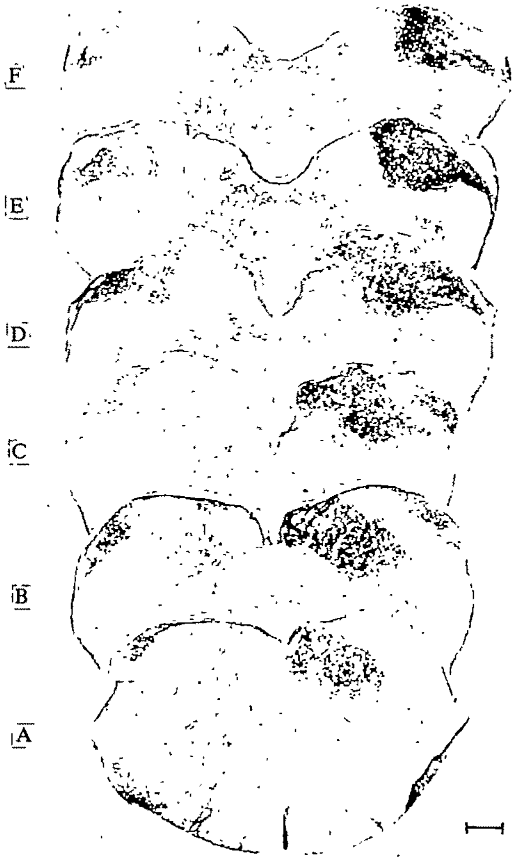

FIG. 2. Bright-field photomicrographs of evenly spaced (800 μm) sections through the medulla of Monkey 29. Neurons are labelled in the DCN contralateral to the HRP injection in the thalamus. Note the presence of labelled neurons also in the external cuneate nucleus as reported by Albe-Fessard *et al.* (1975). Hanker-Yates substrate, light counterstaining with 0·1 per cent cresylechtviolet. Calibration: 1 mm. For finer detail, see Plate 1 (p. 125).

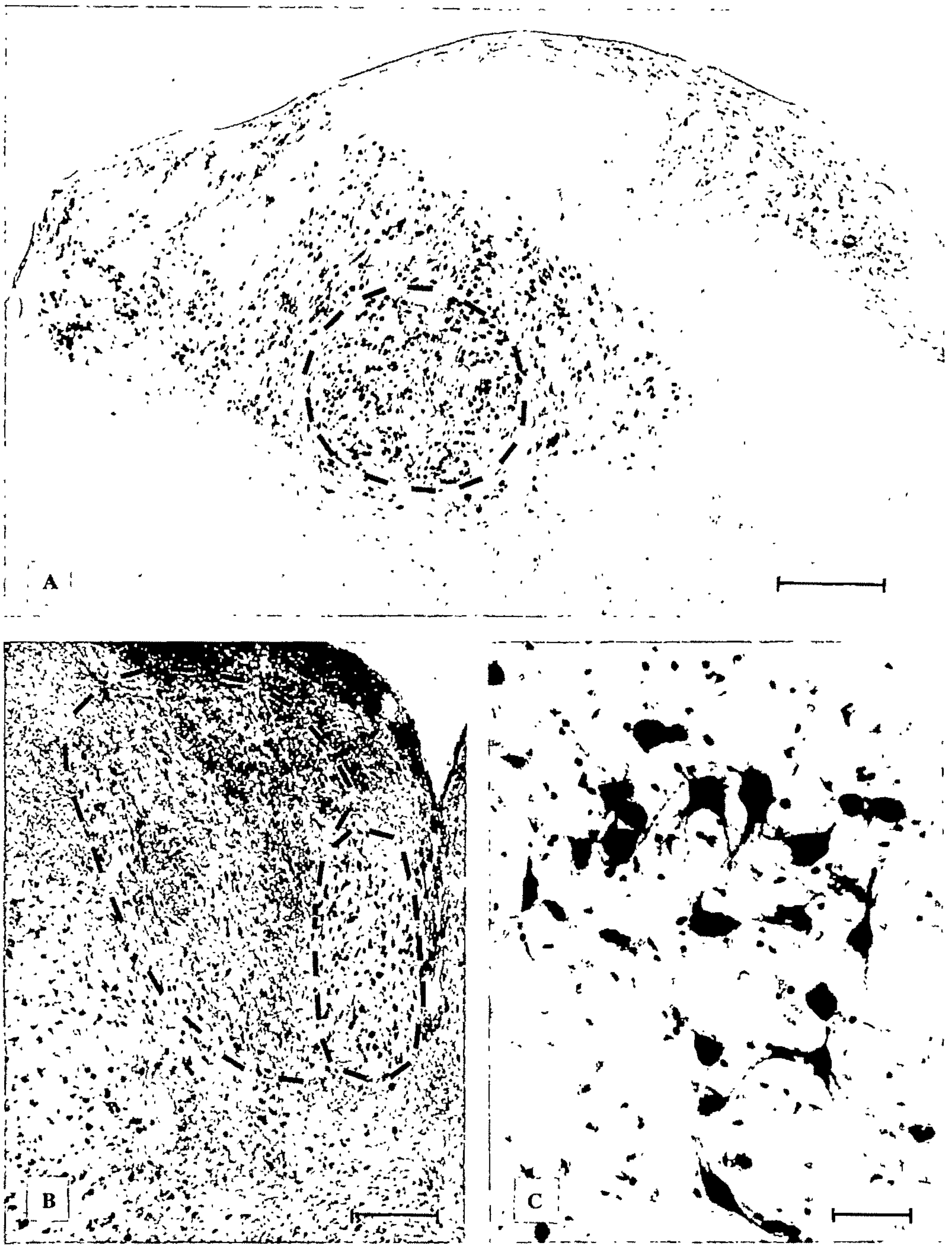

FIG. 3. A, detail of section B of Fig. 2 showing pars rotunda in the cuneate n.; B, pars medialis and pars lateralis of the gracile n. are outlined in a section of the medulla of an unoperated monkey. Klüver-Barrera stain; C, a cluster of DCN neurons labelled in the pars rotunda after thalamic HRP injection in Monkey 29. Hanker-Yates reagent. Calibration: A = 500 μm; B = 250 μm; C = 30 μm.

approximate number of labelled DCN neurons are very similar in both cases. Labelled neurons in both gracile and cuneate nuclei have diameters mainly between 15 and 40 μm, but smaller perikarya (10 to 12 μm) may also display HRP-positive granules. Labelled and unlabelled cells whose perikarya have a diameter of 12 μm or more were counted in the six transverse sections in fig. 2. In the cuneate nucleus the ratio between labelled and unlabelled neurons at different levels varies between 3:1 and 7:1, but it does not seem to follow a gradient along the rostro-caudal axis of the nucleus. In the gracile nucleus this ratio tends to decrease at progressively more rostral levels and is as low as 2:1 at the most rostral level sampled (fig. 4).

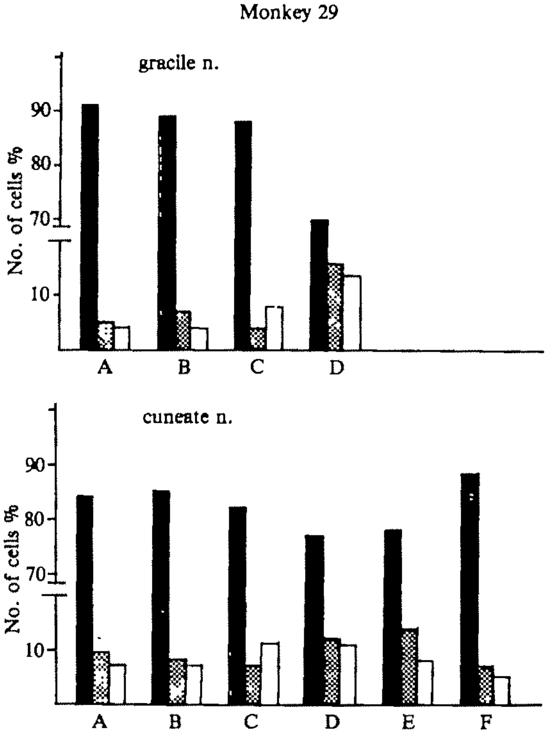

FIG. 4. Percentage of labelled (black columns) and unlabelled DCN neurons with a perikaryal diameter $\geqslant 12\,\mu$m in sections A to F of Monkey 29 with thalamic injection of HRP (*see* fig. 2). The population of unlabelled neurons has been separated into 'small' ($\geqslant 12$ to $<18\,\mu$m, stippled column) and 'large' ($\geqslant 18\,\mu$m, blank column). Letters at bottom of histogram indicate the section of fig. 2 from which counts have been taken.

gracile n.

Labelled : Unlabelled	Ratio	Large (> 18) : Small ($\geqslant$ 12–< 18)	Ratio
A 305: 31	10:1	A 18:13	1:1
B 286: 36	8:1	B 22:14	2:1
C 356: 48	7:1	C 16:32	1:2
D 299:126	2:1	D 68:58	1:1

cuneate n.

Labelled : Unlabelled	Ratio	Large (> 18) : Small ($\geqslant$ 12–< 18)	Ratio
A 321: 61	5:1	A 36:25	1:1
B 732:125	6:1	B 71:55	1:1
C 726:155	5:1	C 62:93	1:2
D 506:152	3:1	D 79:73	1:1
E 821:238	4:1	E 151:87	2:1
F 754:105	7:1	F 62:43	1:1

Labelled neurons as well as small and large unlabelled cells are uniformly distributed throughout the nuclei, as indicated by the fact that when counts are made separately for each nuclear subdivision (fig. 5), ratios are comparable to those obtained for the whole nuclei. Although some of the unlabelled neurons may be thalamic projecting neurons whose terminals did not incorporate a sufficient amount of HRP for neuronal labelling, the large volume (10 μl) of enzyme injected in each monkey was probably sufficient to minimize the number of such neurons.

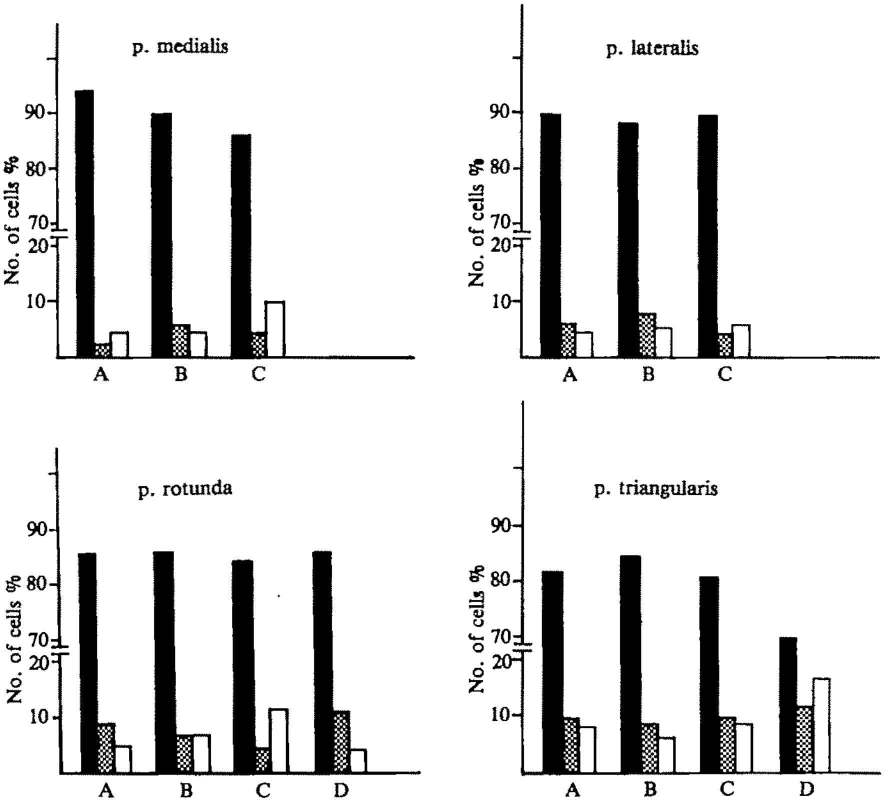

FIG. 5. *See* text.

Non-primary Afferents to the DCN

Selective interruption of non-primary fibres ascending in the dorsal columns from L2 to L6 was achieved by the bilateral lesion of the dorsal funiculus at L1-L2 in Monkey 14 (fig. 6). The slight encroachment by the lesion upon the medial part of the dorsal horn of both sides may have interrupted very few fibres ascending in other parts of the white matter besides the dorsal columns, but degeneration resulting from such damage is probably negligible.

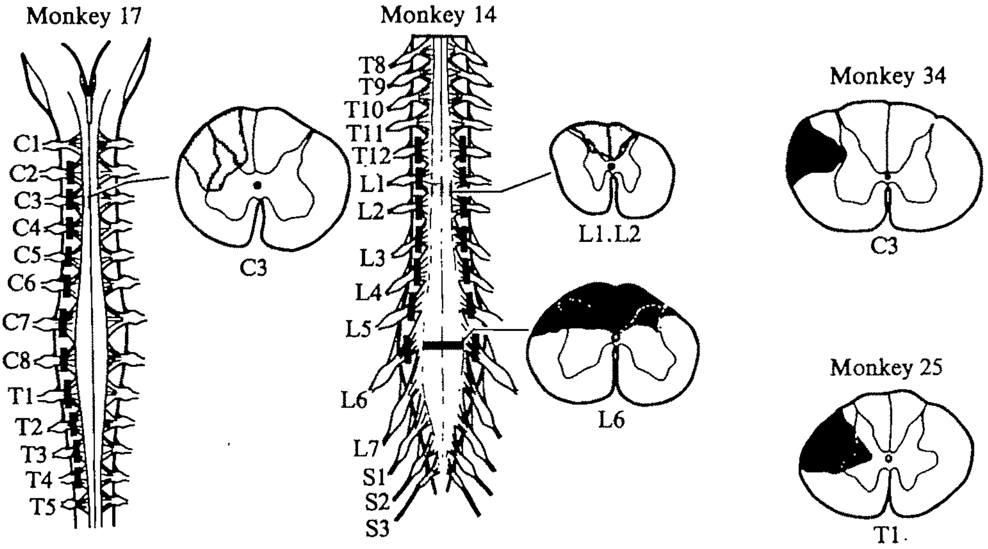

FIG. 6. Schematic reconstruction of the location and extent of the lesions in the spinal cord of 2 monkeys (14 and 17) in which the successive degeneration technique was employed for tracing non-primary afferents to the DCN ascending in the dorsal columns and of monkeys (25 and 34) with dorsolateral funiculus lesion. *See* Material and Methods for further details.

The distribution of degenerating fibres and their terminals in the medulla of this monkey is reconstructed in fig. 7. Degenerating fibres ascend in the fasciculus gracilis in the medulla bilaterally and distribute throughout the length of the gracile complex on both sides. Intranuclear degeneration is sparse at levels through the pyramidal decussation, but it increases at progressively more rostral levels. In sections in which grm and grl are distinguishable (fig. 7B, C, D) degeneration appears only slightly denser in grl (*see also* fig. 11B). In the rostral gracile nucleus (grz), degeneration is uniformly dense throughout the nucleus bilaterally (fig. 7E, F). With the exception of a minor spill-over of degeneration into a small part of the rostral cuneate nucleus (fig. 7E), degeneration is not present in any other medullary nucleus.

The distribution pattern of non-primary afferents originating from spinal levels below T1 and ascending in the dorsal part of the lateral funiculus is documented in Monkey 25 and reconstructed in fig. 8. In this case, no degeneration was evident in the gracile and cuneate fasciculi at medullary levels; this allows exclusion of the possibility that degeneration in the DCN of this animal may be due to accidental damage to dorsal root fibres or dorsal columns at the time of the surgical intervention. Instead, degenerated fibres are present at the level of the pyramidal decussation in the lateral funiculus of the medulla on the side ipsilateral to the lesion. At more cranial levels, they shift progressively more dorsally and are found among fibres contributing to the restiform body. Only a limited number of

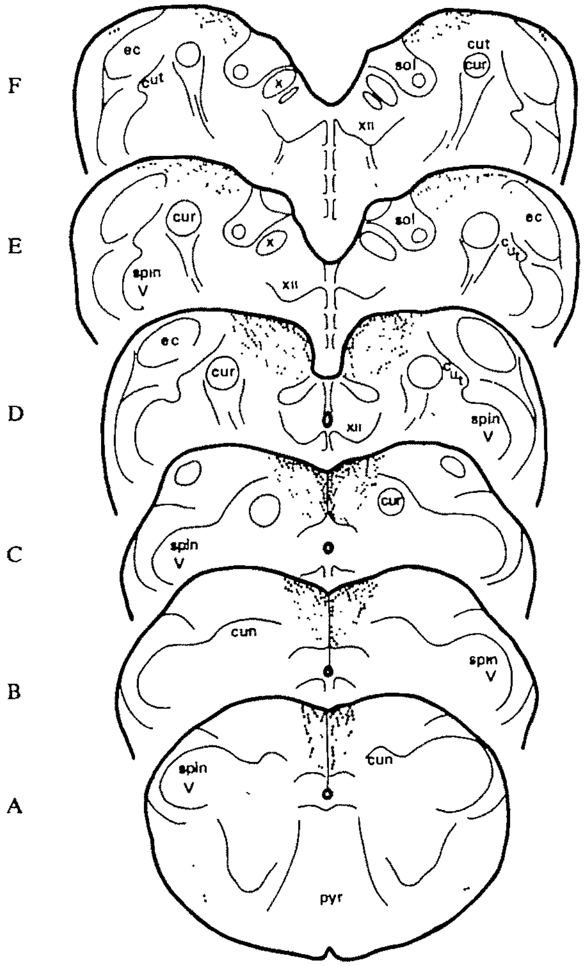

Fig. 7. Graphic reconstruction of the distribution of degeneration in the medulla of Monkey 14 with bilateral interruption of non-primary afferents arising from L2 to L6 and ascending in the dorsal columns.

degenerated fibres are directed dorsomedially through the medullary tegmentum; of these, very few probably reach the DCN. Degenerated fibres ascending via the restiform body invade the grz, where they terminate diffusely (figs. 8D, E and 11A), but also reach part of the rostral cuneate nucleus and the external cuneate nucleus (mainly its dorsolateral) part. Degenerated fibres and their terminals in grm and grl are scanty (fig. 8A, B, C) and appear to reach these regions of the nucleus via a rostral loop, that is, by ascending in the restiform body and then turning caudally to descend within the gracile nucleus and/or fasciculus.

The degeneration in the medulla of Monkey 17 is due to interruption, at C3, of several groups of fibres. These include: (a) dorsal root afferents from levels caudal to T4; (b) non-primary afferents to the gracile nucleus ascending in the dorsal and dorsolateral funiculi; and (c) non-primary afferents to the cuneate nucleus ascending in the dorsal and dorsolateral funiculi. However, for the reasons discussed in Material and Methods, degeneration in the cuneate nucleus and in the external cuneate nucleus of Monkey 17 can be considered almost exclusively due to interruption of non-primary afferents. Degenerated fibres ascend in the dorsal and lateral funiculi in the medulla on the side ipsilateral to the lesion (fig. 9). In the cuneate nucleus degeneration spares the pars rotunda but distributes to the nuclear region surrounding it (pars triangularis) (fig. 11c). At levels through the rostral pole of the cuneate nucleus, where pars rotunda and pars triangularis are no longer distinguishable, degeneration is dense throughout the nucleus (fig. 9F, G). Degeneration is also present, although in moderate amount, in the external cuneate nucleus. In view of the simultaneous involvement, in this case, of dorsal and dorsolateral funiculi, it is difficult to attribute the degeneration in

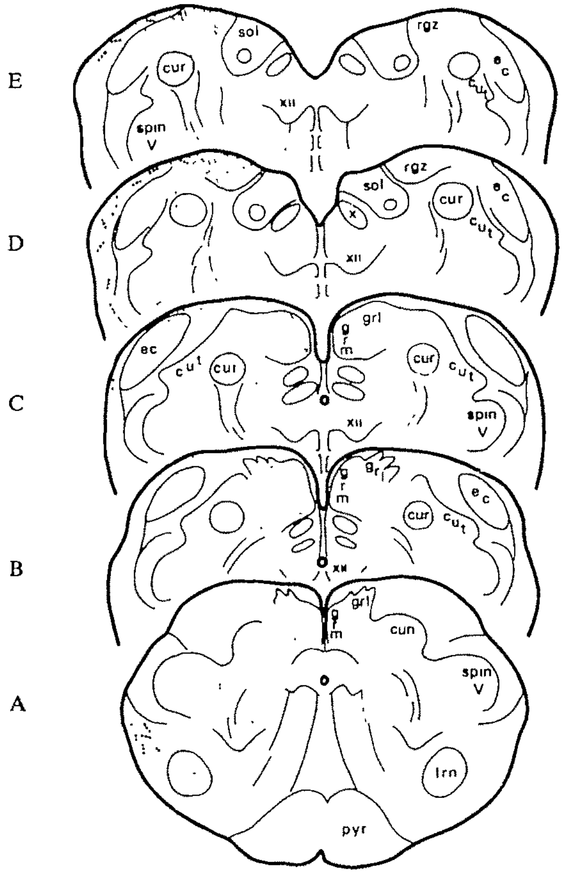

FIG. 8. Graphic reconstruction of the distribution of degeneration in the medulla of Monkey 25 with a lesion of the left dorsolateral funiculus at T1.

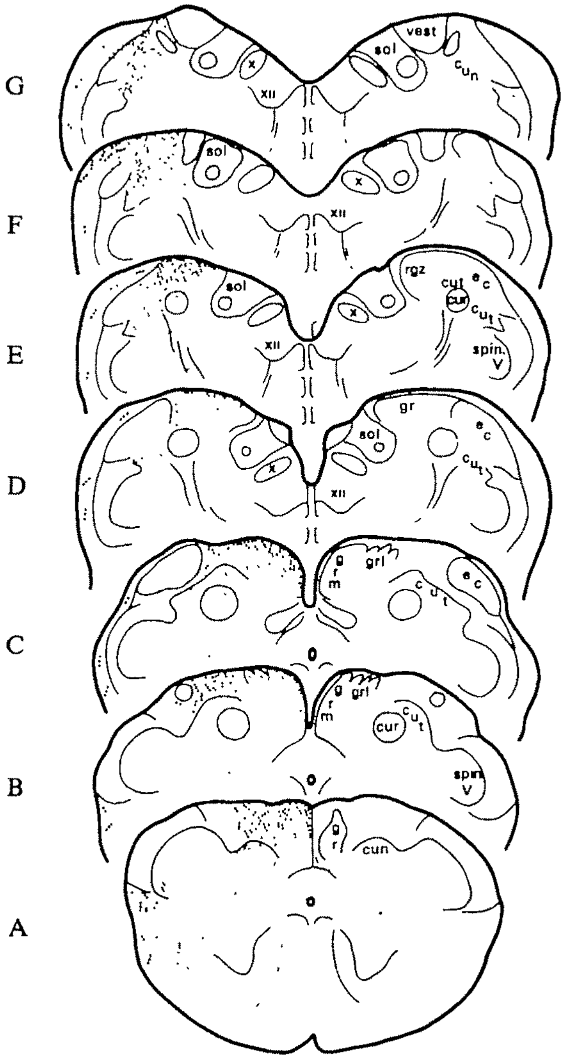

FIG. 9. Graphic reconstruction of the distribution of degeneration in the medulla of Monkey 17. Degeneration in the gracile n. is due to interruption of primary as well as non-primary afferents. In the cuneate n. degeneration is almost exclusively due to interruption of non-primary afferents (*see* fig. 6 and text for further explanation).

different parts of the cuneate nucleus and in the external cuneate nucleus to a lesion of one or the other funiculus. However, from a comparison with Monkey 34, with a lesion of the dorsolateral funiculus only (*see below*), it appears that degeneration in the rostral part of the cuneate nucleus is mainly due to interruption of fibres in the dorsal columns and that non-primary afferents reach the external cuneate nucleus mainly via the dorsolateral funiculus of the cervical spinal cord.

The lesion in Monkey 34 was performed to outline the distribution of non-primary afferents to the DCN originating from levels below C3 and ascending in the dorsal part of the lateral funiculus. The results in this animal are in good agreement with those reported by Nijensohn and Kerr (1975). The bulk of the degenerated fibres ascend in the ipsilateral lateral funiculus of the medulla (fig. 10). As in Case 25, absence of degenerating fibres in the dorsal columns at most caudal medullary levels allows exclusion of the possibility that degeneration may be due to inadvertent damage of dorsal root fibres and/or dorsal columns during the surgical operation on the dorsolateral funiculus. From the medullary lateral funiculus, fibres course dorsomedially through the tegmentum but also dorsally into the restiform body. Terminal degeneration in the DCN is sparse at caudal medullary levels (fig. 10A, B), but starting from levels slightly below the obex, it distributes to the gracile nucleus and to the pars triangularis of the cuneate nucleus (fig. 10C–F). Degeneration extends rostrally to the end of the gracile and cuneate

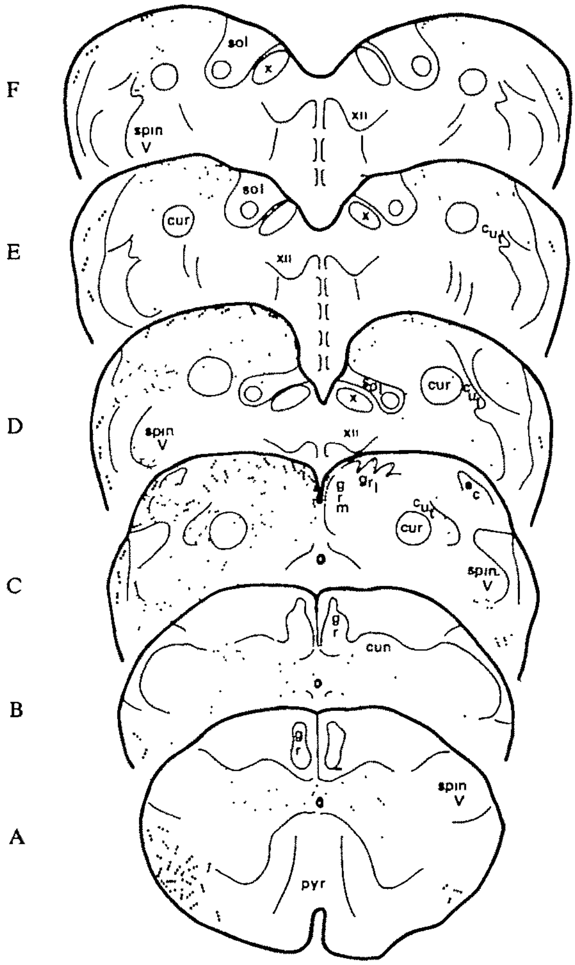

FIG. 10. Graphic reconstruction of the distribution of degeneration in the medulla of Monkey 34 with a lesion of the left dorsolateral funiculus at C3.

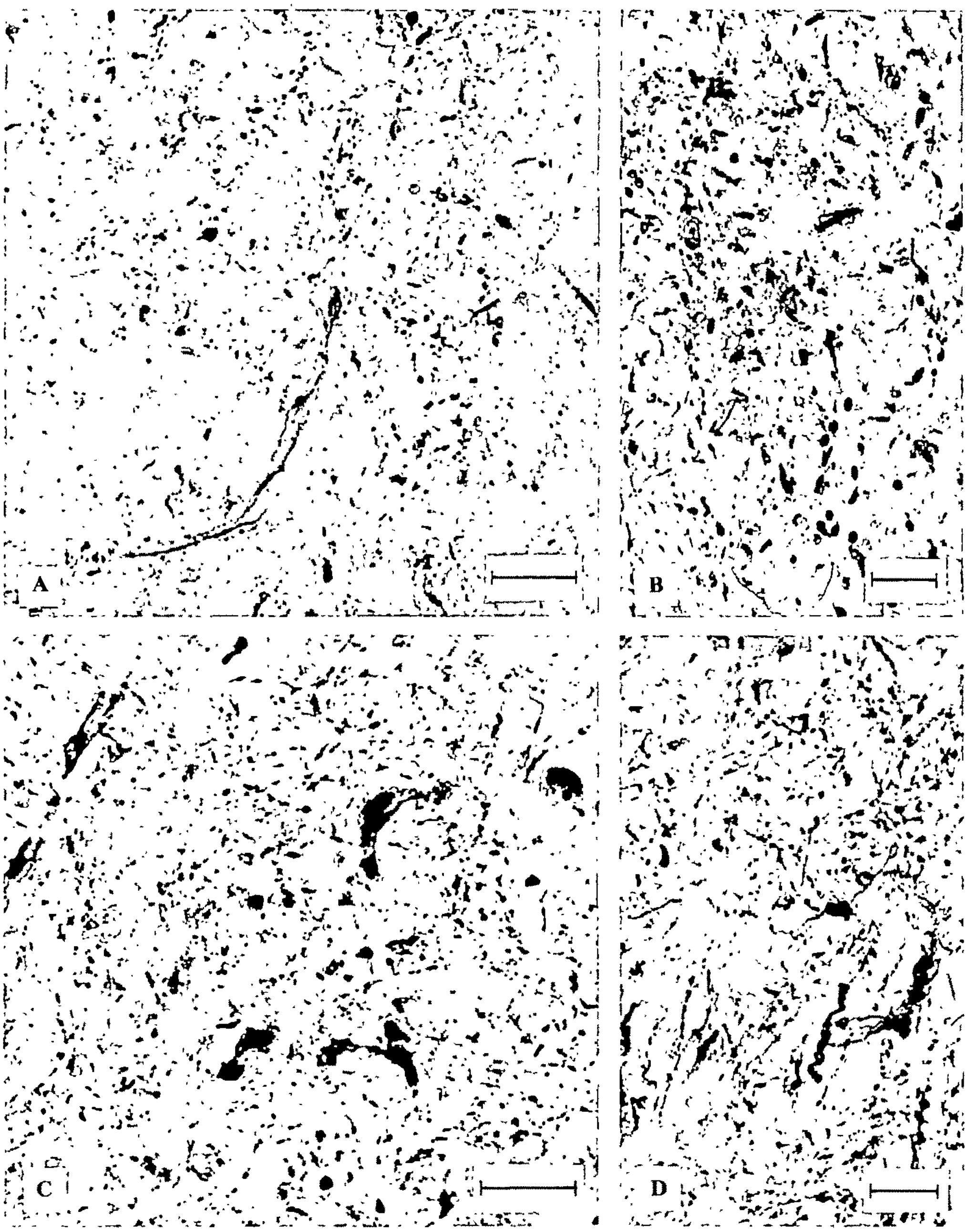

FIG. 11. Photomicrographs showing the density of degenerated elements impregnated according to the Fink-Heimer technique. A, rostral gracile-nucleus Z complex of Monkey 25; B, pars lateralis of the gracile n. of Monkey 14; C, pars triangularis of the cuneate n. of Monkey 17; D, external cuneate n. of Monkey 34. Calibration: 30 μm.

nuclei and is also present throughout all levels of the external cuneate nucleus (figs. 10 and 11D). Degeneration in the medulla on the side contralateral to the lesion is probably due to crossing at spinal levels, since degenerated fibres are present in the lateral funiculus of the medulla already at the level of the pyramidal decussation.

Autoradiographic techniques have also been employed to trace non-primary afferents in the DCN. The location and spread of the injection of tritiated amino acids in the spinal cord of 4 monkeys is reconstructed in fig. 12. In 2 monkeys (27 and 30), the focus of the injection is in the left dorsal horn at L4 to L6 (Case 27) and at L4 and L5 (Case 30). The distribution of reduced silver grains in the emulsion overlying the sections of medulla in these 2 monkeys is very similar. Autoradiographic silver grains over the gracile nucleus ipsilateral to the injection are sufficiently numerous to suggest that spinal fibres, even from only two or three lumbar levels, represent a conspicuous projection system to this nucleus. Also, when comparing the distribution of grains over fibre tracts, it appears that the gracile fasciculus represents the main path followed by these ascending fibres to

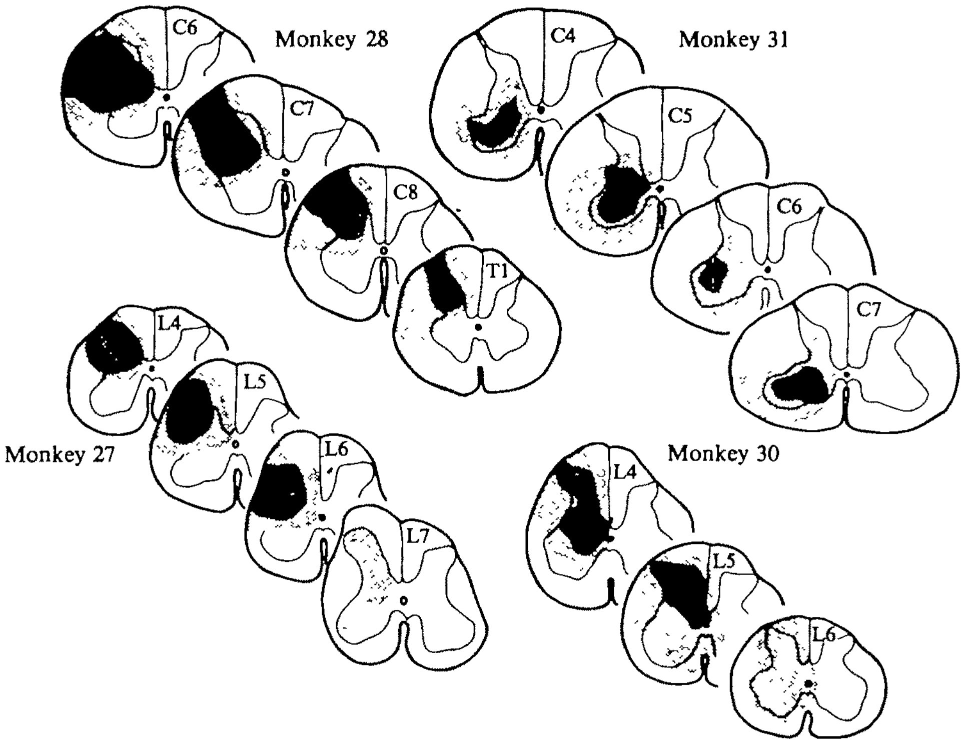

FIG. 12. Reconstruction of the maximal extent of the spinal injection of tritiated amino acids as revealed by the density of autoradiographic silver grains in 4 monkeys. Areas heavily labelled with radioactive tracer are represented in black; less intense labelling is indicated with stippling. A restricted area of tissue necrosis occupies the centre of the focus of the injection at L4 in Monkey 27.

reach the homonymous nucleus. These observations are in agreement with the degeneration results described above, although silver grains are more numerous over pars medialis than pars lateralis of the left gracile nucleus of Monkey 30 (fig. 13). On the side of the medulla contralateral to the injection, silver grains above background overlie only the lateral funiculus.

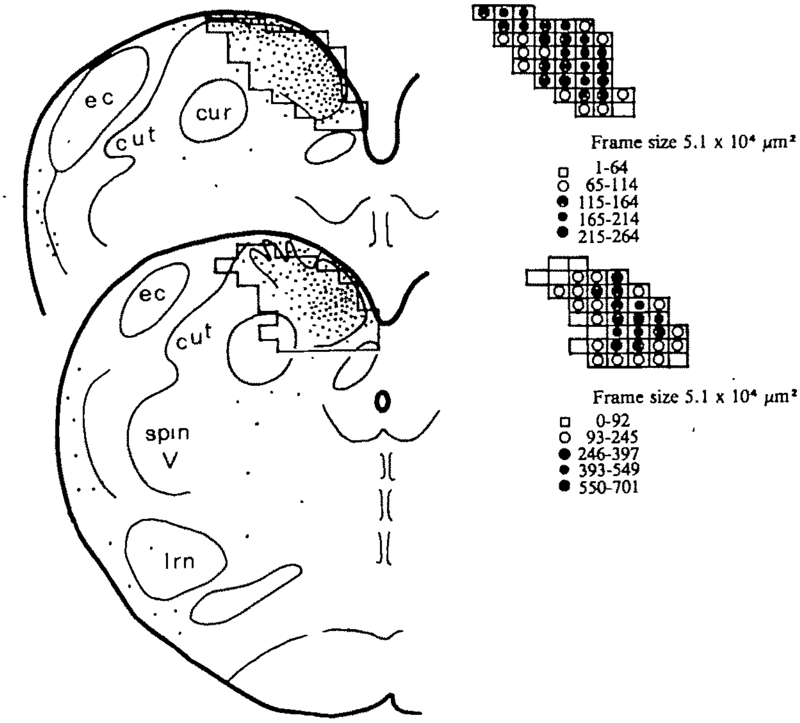

FIG. 13. Diagrammatic reconstruction of grain distribution and automated grain counts over two sections of the left medulla of Monkey 30.

In Monkey 28 the injection of tritiated amino acid was aimed at the dorsal horn of the brachial cord for tracing non-primary afferents to the DCN from these spinal cord levels. The injected tracer is concentrated in the dorsal horn, the dorsolateral funiculus and part of the intermediate zone on the left side at C6 to T1. On the left side of the medulla of this monkey, autoradiographic silver grains overlie the lateral funiculus and the cuneate fasciculus. At the level of the pyramidal decussation, silver grains are mainly present over the lateral reticular nucleus, and only a few grains are scattered over the cuneate nucleus. At more rostral levels through this nucleus, silver grains become more numerous and are confined almost

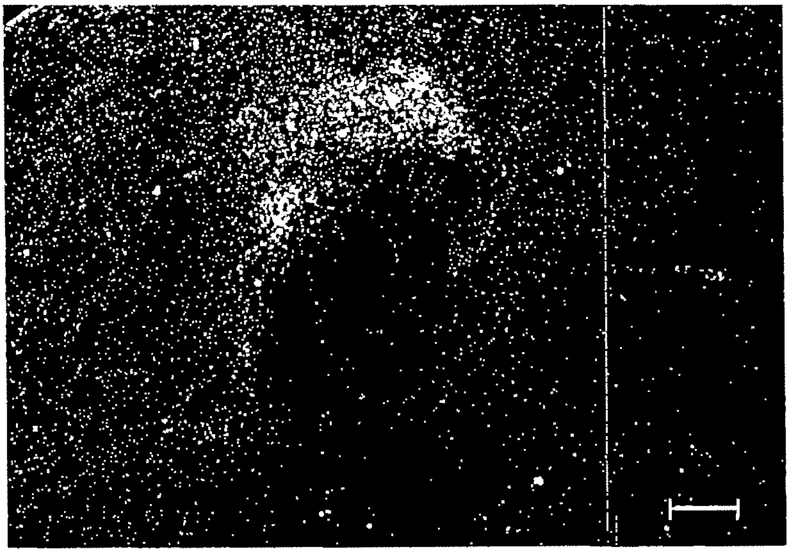

FIG. 14. Dark-field photomicrograph of silver grain distribution over the cuneate n. and surrounding regions in Monkey 28. This picture has been taken from a section at a medullary level comparable to level E in fig. 9. Note the similarity in the distribution of autoradiographic silver grains and Fink-Heimer degeneration (fig. 9D and E). Calibration 200 μm.

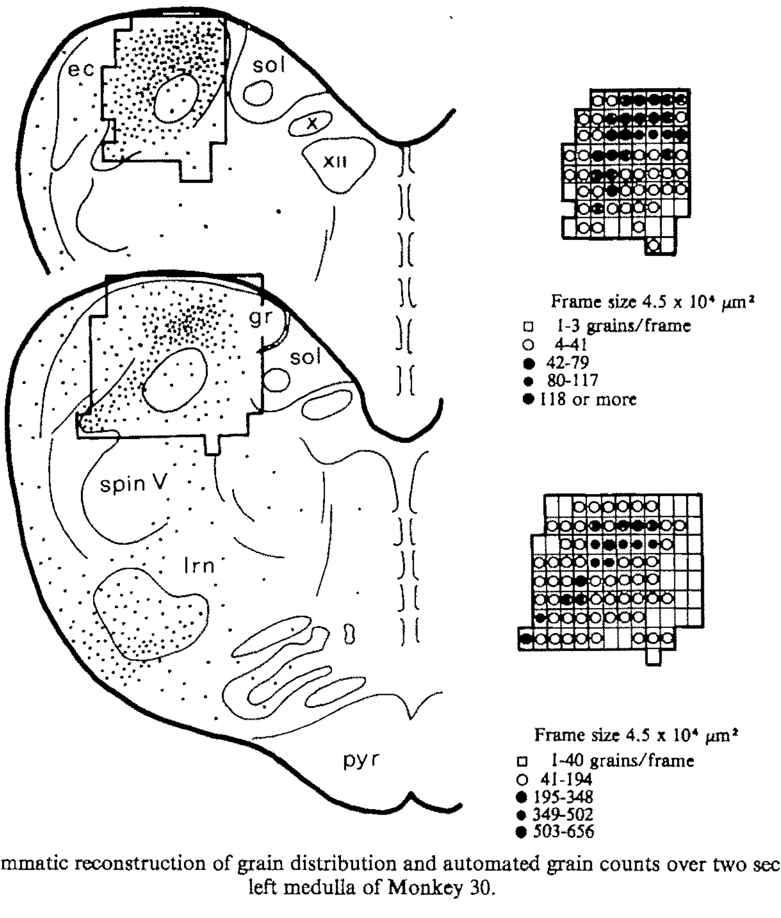

FIG. 15. Diagrammatic reconstruction of grain distribution and automated grain counts over two sections of the left medulla of Monkey 30.

exclusively to the pars triangularis (figs. 14 and 15). The relative sparing of the pars rotunda, as shown by autoradiographic techniques, closely matches the results with the Fink-Heimer method. Silver grains over the left external cuneate nucleus become more numerous at progressively more rostral levels through this nucleus and are rather uniformly distributed.

On the side of the medulla contralateral to the site of the injection, silver grains clearly above background label fibre tracts in the lateral funiculus.

In Monkey 31, in which the injection was mainly placed in the ventral gray at all levels involved (C4 to C7), silver grains were virtually absent from the DCN, a result which supports the evidence that the origin of non-primary afferents from the brachial cord of monkeys is confined to the dorsal horn (*see below*).

Cells of Origin of Non-primary Afferents

The results in the 6 cases of fig. 16 have been summarized in a previous report (Rustioni, 1977). The results in 2 additional monkeys with medullary injection of HRP (32 and 35) are reconstructed in figs. 17 and 18. Labelled neurons in both cases are concentrated in the medial part of the dorsal horn ipsilateral to the injection at upper cervical levels. In the brachial enlargement, labelled cells are most numerous in the medial part of the dorsal horn ventral to the substantia gelatinosa but also spread through a band of gray matter largely corresponding

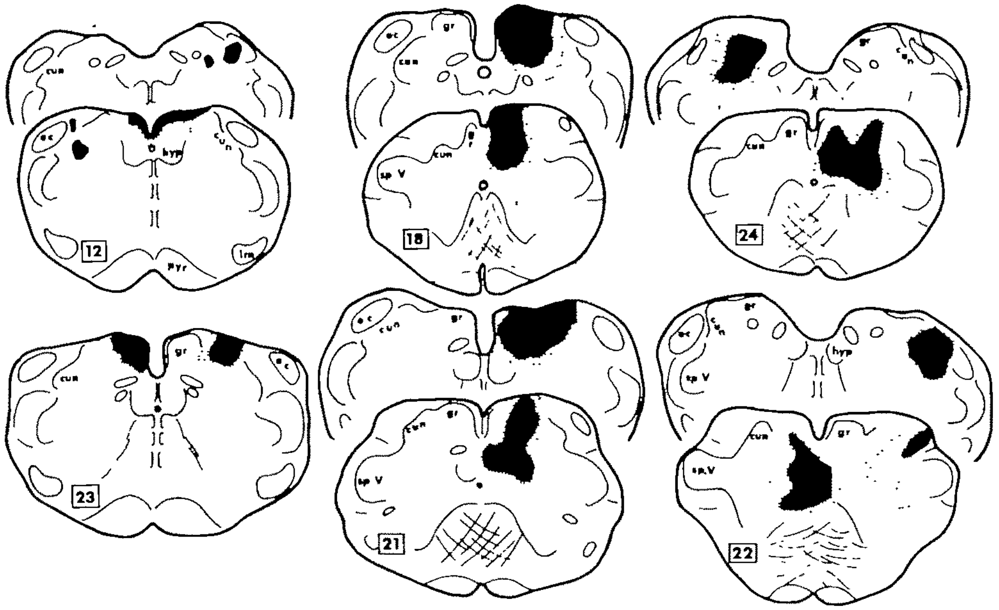

FIG. 16. Reconstruction of the maximal extent of reaction product consequent to HRP injections in the dorsal medulla of 6 *macaques*. Areas displaying an intense reaction product are represented in black; less intense reaction product is indicated with stippling.

to lamina IV of the spinal cord of the cat. Labelled cells are relatively sparse in thoracic segments below T1 and numerous again throughout lumbosacral segments. At these levels, as in the brachial enlargement, labelled cells are concentrated in 'lamina IV' but are also found in other dorsal horn laminæ. Labelled cells in the dorsal horn throughout all segments examined have perikarya, mostly of the multipolar or oval type. Spindle-shaped cell bodies are frequently labelled along the medial margin of the dorsal horn. In segments C6, C7, L6, and L7 of Monkeys 32 and 35, quantitative data have been collected from a band of gray matter containing the bulk of labelled cells in the dorsal horn and extending 250 μm ventral to the uniformly small-celled 'lamina III' (fig. 19). Within the limits of this region, about 80 per cent of labelled neurons have longer diameters ranging from 21 to 40 μm at both cervical and lumbar levels. However, differences between the two

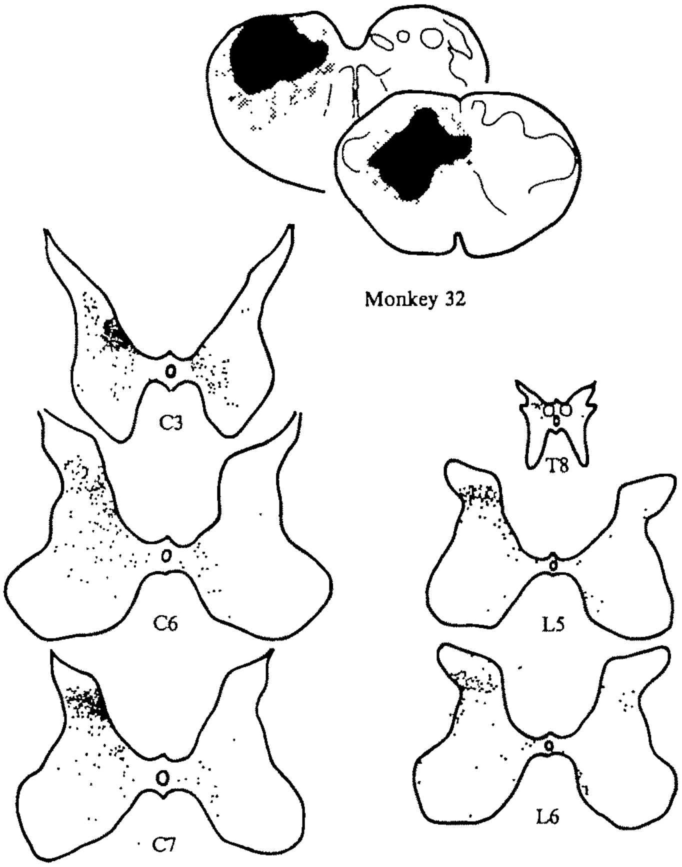

FIG. 17. Reconstruction of the diffusion of injected HRP in the medulla and of labelled cells in the spinal cord of Monkey 32. HRP diffusion in the medulla is represented as in fig. 16. Plottings from 40 randomly selected sections have been superimposed to obtain drawings of each spinal cord segment. One dot corresponds to one labelled cell.

selected cervical and lumbar segments are evident and similar in the 2 monkeys studied when comparing the mediolateral distribution of labelled neurons. At C6–C7, 68·5 per cent (in Monkey 32) and 67 per cent (in Monkey 35) of labelled cells in the strip of gray matter outlined in fig. 19 are in its medial half. In contrast, labelled cells at L6–L7 are mainly present in its lateral half (64 per cent in Monkey 32 and 62 per cent in Monkey 35).

Large cell bodies (up to 65 μm) are labelled, at lumbar levels only, along the lateral margin of the ventral horn ipsilateral to the injection. The heavy involvement, by the injected HRP, of the medullary tegmentum in Monkey 32 may account for the greater number of labelled cells in this case as compared with Monkey 35, especially in the ipsilateral intermediate zone and on the side contralateral to the site of the injection. In both cases other structures besides the DCN

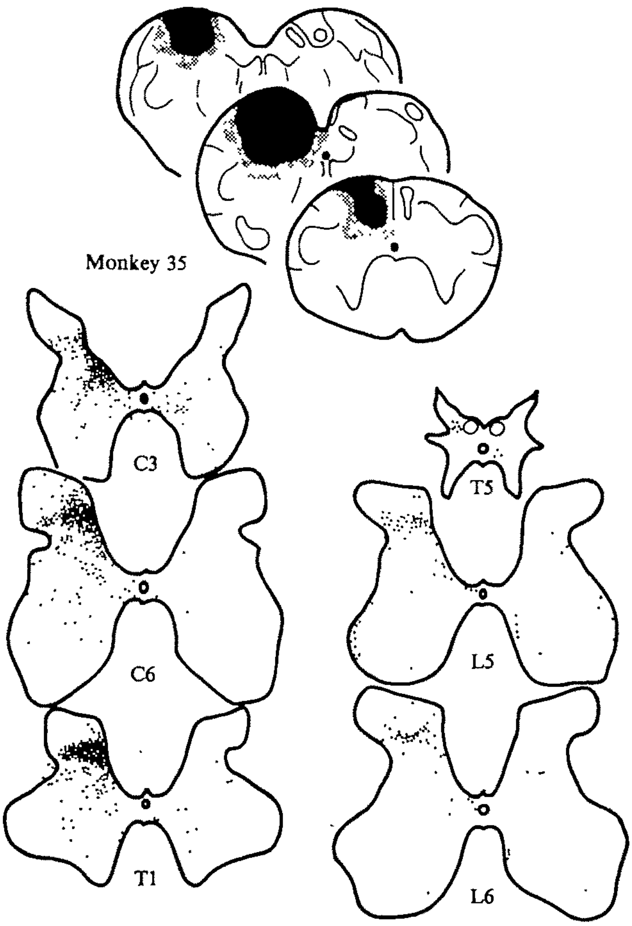

FIG. 18. Reconstruction of the diffusion of injected HRP in the medulla and of labelled cells in the spinal cord of Monkey 35. *See legend* to fig. 17 for further details.

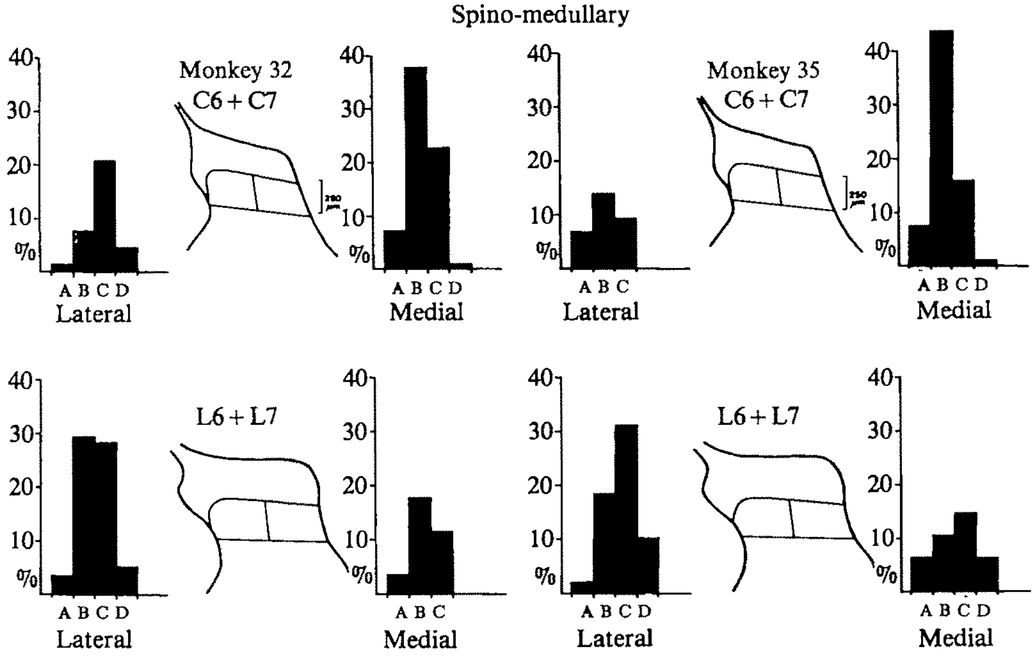

FIG. 19. Counts of labelled neurons in a 250 μm thick region of spinal gray matter lying just ventral to lamina III at C6–C7 and L6–L7 of Monkeys 32 and 35. Neurons are grouped according to perikaryal diameter: A = <20 μm; B = 21 to 30 μm; C = 31 to 40 μm; D = 41 to 50 μm.

have been involved by the HRP injection. However, since it is apparent from the results with degeneration and autoradiography that, in the dorsal medulla of monkeys, the DCN are the main recipients of ascending spinal fibres, it can be assumed that at least a large fraction of labelled cells, even in Monkey 32, are the origin of spino-DCN afferents. Thus, the results in these two monkeys support the conclusion of the previous paper (Rustioni, 1977) in which most animals received restricted injections, that is, that non-primary afferents to the DCN originate from spinal neurons mainly in 'lamina IV' but also spreading into more ventral adjacent laminæ, i.e., 'lamina V' and, especially at upper cervical levels, the medial part of 'lamina VI'.

DISCUSSION

The demonstration of the origin, course and termination of ascending spinal pathways to the DCN of monkeys is the main result of the present work. At the same time, observations on the organization of the primate DCN in unoperated animals and in animals with HRP injections in the thalamus deserve consideration in the following discussion. Cell populations and thalamic projections of the DCN in monkeys have been studied to provide a cytoarchitectonic map upon which to reconstruct the distribution of non-primary afferents and for the purpose of comparing the anatomy of these nuclei in primates with that in cats. In the latter species a dichotomy exists within the anatomical organization of the DCN; this can be briefly summarized by distinguishing two general regions within both the gracile and the cuneate nuclei (Kuypers and Tuerk, 1964). The typical 'lemniscal' portion of these nuclei is formed by clusters of five to ten or more perikarya with characteristic dendrites. These neurons receive their only extrinsic input via dorsal root fibres and project in a highly topographic manner to the nucleus ventralis posterolateralis of the thalamus (Hand and van Winkle, 1977). The clusters region is most dorsally and caudally located in the medulla, and it is adjoined ventrally and caudally by a large population of neurons with perikarya of variable shape and size but mostly of the multipolar type. Dendrites of these neurons are mainly radiating diffusely and bear some resemblance to those of neurons in the medullary reticular formation. Thalamic relay cells are quite sparse among neurons of this type, especially in the rostral DCN (Cheek, Rustioni and Trevino, 1975). With regard to ascending afferents to the feline DCN, rostral and ventral portions of these nuclei differ from the region of the clusters in that only the former two receive non-primary afferents in addition to dorsal root fibres (Rustioni, 1973, 1974). Although the present material does not include Golgi preparations, it suggests that in the DCN of monkeys, as in cats, cytoarchitectonic differences exist, pars medialis (in the gracile nucleus) and pars rotunda (in the cuneate nucleus) being the likely homologues of the cluster region of the feline DCN. This homology receives support from a comparison of the pattern of distribution of dorsal root fibres in the two species (Rustioni and Macchi, 1968; Shriver, Stein and Carpenter, 1968; Carpenter, Stein and Shriver, 1968). However, at variance with cats, thalamic projecting neurons in monkeys appear uniformly distributed throughout the DCN, although within the gracile nucleus their number may decrease at progressively more rostral levels. The identification of regions in the primate DCN which differ with regard to cytoarchitectonics and fibre connections allows one to suggest that the organization of the DCN in macaques may parallel, in some respect, that of the ventrobasal complex and somatosensory cortex in the same species, as interpreted by Whitsel and his associates (Werner and Whitsel, 1973; Loe, Whitsel, Dreyer and Metz, 1977). According to this view, it may be proposed that at all three levels along the somatosensory system, neurons related to the extremities and primarily receiving information about cutaneous events are arranged into a core region surrounded by neuron pools primarily related to proximal parts of the body and mainly activated by subcutaneous receptive fields. Fibre connections of the core differ from those in the surrounding territory at three levels, and these differences may be specifically related to the different functional role of these neuronal subsets (Whitsel, Rustioni, Dreyer, Loe, Allen and Metz, 1978). Although electrophysiological data on the primate DCN are virtually non-existent, unit recordings in raccoons (Johnson, Welker and Pubols, 1968) are in general agreement with the above proposition.

Non-primary afferents to the monkey DCN ascend in both the dorsal columns and dorsal part of the lateral funiculus. Although no experiment has been carried out, in the present work, to test whether non-primary afferents to the DCN of monkeys may ascend elsewhere in the spinal white matter, this question can be answered negatively on the basis of other reports with degeneration techniques (Mehler, Feferman and Nauta, 1960; Kerr, 1975). Both degeneration and autoradiographic approaches suggest that indirect ascending afferents to the gracile and cuneate nuclei are more numerous in the dorsal columns than in the dorsolateral funiculus. Further, some qualitative differences exist when comparing the distribution pattern of non-primary afferents in these two parts of the spinal white matter. Non-primary afferents ascending to the gracile nucleus in the dorsal columns are distributed, although not uniformly, throughout the entire caudo-rostral extent of this nucleus. Concerning the relative concentration of terminals of these afferents in the pars medialis as compared to pars lateralis of this nucleus, results with degeneration and anterograde transport are somewhat different. This difference may be related to the visualization of non-primary afferents from a larger number of lumbar segments in the Fink-Heimer experiment as compared with the autoradiographic material. Although it cannot be excluded that terminal degeneration is not adequately visualized in the pars medialis of the gracile nucleus, and/or that chronic deafferentation may have induced some rearrangement of fibres and terminals in the gracile nucleus, these explanations for the differences in the degeneration and autoradiographic material are unlikely in view of the close correspondence of the results with the two approaches in the cuneate nucleus (*see below*).

Non-primary afferents ascending in the lateral funiculus below T1 terminate almost exclusively in the rostral gracile-nucleus Z complex. These afferents are likely to mediate input from deep receptors in the hindlimb. That this may be the case is suggested by the electrophysiological work by Whitsel, Petrucelli and Sapiro (1969) who found that cutaneous and deep (including muscle) afferents are present in the lumbar dorsal columns of squirrel monkeys, but only cutaneous first-order fibres ascend in the fasciculus gracilis at cervical levels. More recently, Dostrovsky and Millar (1977) have recorded the response of gracile neurons of cats with transected dorsal columns. In agreement with the above observations, they suggested that ascending paths to the gracile nucleus in the lateral funiculus mediate information related to deep receptive fields and joint movements. In addition to these modalities, however, high-threshold mechanical or noxious stimuli are also mediated by spino-gracile fibres in the lateral funiculus of cats (Dart and Gordon, 1973; Dostrovsky and Millar, 1977). These data are of special interest, if applicable to primates, as a tentative explanation for the relief of pain observed in patients with cordotomies destroying the dorsolateral quadrant (Moffie, 1975).

The distribution pattern of non-primary afferents from brachial levels is very similar when degeneration and autoradiographic material are compared. Non-primary afferents from these levels distribute to the pars triangularis and rostral region of the cuneate nucleus and to the external cuneate nucleus. From a comparison of the results in different animals it appears that non-primary afferent fibres terminating in the rostral part of the cuneate nucleus are particularly numerous in the dorsal columns, while indirect afferents to the external cuneate nucleus are primarily supplied via fibres ascending in the dorsal part of the lateral funiculus. Within the cuneate nucleus ascending fibres from cervical and uppermost thoracic spinal segments spare the central core (pars rotunda) which contains an expanded representation of dorsal root fibres innervating distal portions of the forelimb (Shriver, Stein and Carpenter, 1968). In contrast, the same afferent pathways appear more directly linked to nuclear regions in which proximal parts of the upper limb are represented (pars triangularis) and to the rostral cuneate where all upper limb dermatomes are somatotopically represented, each in narrow, largely overlapping bands. In cats, the rostral region of the cuneate nucleus differs from the clusters region in that the former is characterized by spatial and modal convergence, while neurons in the latter region have small receptive fields and are most typically responsive to cutaneous stimulation and especially hair receptor discharge (Gordon and Jukes, 1964). Anatomical aspects of the afferent input to the rostral cuneate suggests that this nuclear region may be similarly organized in cats and in monkeys. However, when the ratio of labelled to unlabelled neurons in this region in monkeys (5:1) is compared with that in cats (1:1, unpublished observations), it is apparent that a higher proportion of neurons in the rostral cuneate n. projects to the thalamus in primates than in carnivores. Although these data are derived from only a few experiments and may be subjected to some criticism, they seem to indicate that the higher degree of functional specialization of the monkey's extremities, especially the upper ones, is associated with the input from the whole DCN being, in this species, more directly channelled to the thalamus and thus the cerebral cortex than in cats. For the purpose of the present discussion, perhaps the most relevant consequence of the above comparative aspects of the anatomy of the DCN is that whatever information non-primary afferents mediate, this is likely to exert a stronger influence on somatosensory cortical functions in primates than in carnivores.

The location of cells of origin of non-primary afferents to the DCN in monkeys is very similar to that of the same cells in cats. However, cell counts from spinal cord sections of animals with comparable medullary injections and processed with identical methods suggest that spino-DCN neurons are about twice as numerous in the dorsal horn of monkeys as compared to cats. Furthermore, labelled neurons along the lateral part of the ventral horn ipsilateral to the injection are regularly observed in the lumbar cord of monkeys with medullary injections but never in cats with similar injections (but *see* Molenaar, 1977). For the purpose of topographical description of spinal neurons, Rexed's laminæ are the most convenient reference (Rexed, 1952). Some caution should nevertheless be used when identification of such laminæ is attempted in species other than cat and in histological sections which, in common routine, are much thinner than those employed by

Rexed for his original description. In the spinal grey matter of monkeys, while the border between 'lamina III' and 'lamina IV' is relatively easy to identify, it is harder to draw a separation between 'lamina IV' and 'lamina V'. This is especially so since even in cats lamina IV's 'ventral border is . . . sometimes diffuse, especially laterally, where lamina V also has many large cells' (Rexed, 1952). For these reasons, although it may be confidently stated that the majority of spino-DCN neurons in monkeys are in 'lamina IV', many of them may be quite appropriately attributed to 'lamina V'. The question takes relevance from the body of recent electrophysiological evidence which supports a functional differentiation of these two laminæ (Kerr, 1978). According to this evidence, in lamina V are concentrated neurons responding to a wide variety of intensities of stimuli, including those in the noxious range, while cells in lamina IV are most characteristically fired by impulses originating from low-threshold mechanoreceptors. 'Laminæ IV and V' of the monkey spinal cord contain not only spino-DCN neurons but also spinocervical and spinothalamic neurons. A possible common origin for at least some spino-DCN fibres in the dorsolateral funiculus and spinocervical tract fibres in cats has been discussed by Dart and Gordon (1973), Angaut-Petit (1975) and Rustioni and Kaufman (1977). In support of a possible complex branching of the axon of spinal neurons are the observations by Ramón y Cajal (1952), generally supported by more recent studies of neurons with bifurcating axons in the dorsal part of the spinal grey matter and entering different spinal funiculi on the same side or on both sides of the cord. Collateral branches of spinocervical neurons in lamina IV have been demonstrated by Snow, Rose and Brown (1976) and by Rastad, Jankowska and Westman (1977) in cats; although in their material, these collaterals could be followed for only a short distance, it is not unlikely that a dorsal horn neuron may give rise, by way of collaterals, to fibres contributing to more than one ascending pathway. Preliminary quantitative data on the morphology and distribution of spinothalamic and spino-DCN neurons in the monkey's 'laminæ IV and V' (unpublished observations) are compatible with such an hypothesis. The existence of neurons of which the axon branches and contributes to the dorsal columns and to the spinothalamic tract is especially likely at lumbosacral levels where cells of origin of both pathways are concentrated in the lateral part of these laminæ. The question of collateral branching of ascending spinal neurons is now being approached with a recently introduced technique for double-labelling of central neurons (Hayes and Rustioni, 1978).

Interpretations of the functional aspects of the dorsal columns have stressed the uniqueness of this ascending pathway with regard to its transmission of direct input from the periphery to a supraspinal centre. The present results, however, provide evidence that in primates, as already demonstrated in cats, an additional pathway ascends in the dorsal columns and that it takes origin from neurons likely to mediate a wide range of sensory modalities, including noxious stimuli. One of the most immediate functional implications of such an anatomical arrangement is that information integrated at spinal levels may modulate the discharge of DCN neurons in response to dorsal root afferent input. The likelihood that such a modulatory influence is directly accessible to corticospinal fibres terminating in the dorsal horn provides a mechanism by which the sensorimotor cortex may control DCN functions not only via cortico-DCN fibres but also by interposition of spinal neurons. Furthermore, it should be stressed that, on the basis of the location of cells of origin of spino-DCN fibres and by extrapolation from electrophysiological data in cats, postsynaptic fibres in the dorsal columns of monkeys may be responsive to noxious and, perhaps, thermal stimuli (Uddenberg, 1966; Angaut-Petit, 1975) and thus play some subtle role in the appreciation of sensory modalities which are primarily associated with the anterolateral quadrant of the spinal cord (Dennis and Melzack, 1977). Such a proposition is consonant with the idea that a specialized role for each ascending pathway is compatible with some degree of functional overlap (Brown and Gordon, 1977), and it may account, at least in part, for the elusiveness of the interpretation of deficits consequent to interruption of individual ascending pathways of primates.

SUMMARY

Cell populations and thalamic projections of the dorsal column nuclei in macaques have been investigated in the medullæ of normal animals and of animals with injections of horseradish peroxidase in the nucleus ventralis posterolateralis. In the same species, the course, distribution and origin of ascending non-primary pathways to the dorsal column nuclei have been demonstrated with the aid of degeneration methods, ^{3}H-amino acid autoradiography and retrograde axonal transport of horseradish peroxidase. Non-primary afferents to the gracile and cuneate nuclei ascend mainly in the dorsal columns and, to a lesser extent, in the dorsal part of the lateral funiculus. Afferents originating from lumbar segments and ascending in the lateral funiculus terminate mainly in the rostral part of the gracile nucleus while those ascending in the dorsal columns distribute throughout most of the rostrocaudal extent of the same nucleus. Afferents from brachial levels terminate mainly in the cuneate nucleus and in the external cuneate nucleus. Degeneration and autoradiographic material concurrently demonstrate that non-primary afferents to the cuneate nucleus terminate preferentially within certain cytoarchitectonic subdivisions of this nucleus. Ascending spinal afferents to the dorsal column nuclei originate mainly from the ipsilateral dorsal horn, particularly from its medial part at upper cervical levels and from a band of gray, throughout the cord, largely corresponding to lamina IV and adjacent laminæ. Large neurons along the lateral border of the ventral horn at lumbar levels may also contribute non-primary afferents to the ipsilateral dorsal column nuclei. These anatomical results provide some cues to a revised view of the organization of the dorsal column nuclei in monkeys and, taken together with recent electrophysiological and clinical data, contribute to a re-evaluation of some functional aspects of the dorsal column-medial lemniscal system of primates.

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REFERENCES

ALBE-FESSARD, D., BOIVIE, J., GRANT, G. and LEVANTE, A. (1975) Labelling of cells in the medulla oblongata and the spinal cord of the monkey after injections of horseradish peroxidase in the thalamus. *Neuroscience Letters*, **1**, 75–80.

ANGAUT-PETIT, D. (1975) The dorsal column system. II. Functional properties and bulbar relay of the postsynaptic fibers of the cat's funiculus gracilis. *Experimental Brain Research*, **22**, 471–493.

BECK, C. H. M. (1976) Dual dorsal columns: a review. *Canadian Journal of Neurological Sciences*, **3**, 1–7.

BIEDENBACH, M. A. (1972) Cell density and regional distribution of cell types in the cuneate nucleus of the Rhesus monkey. *Brain Research, Amsterdam*, **45**, 1–14.

BOIVIE, J. (1978) Anatomical observations on the dorsal column nuclei, their thalamic projection and the cytoarchitecture of some somatosensory thalamic nuclei in the monkey. *Journal of Comparative Neurology*, **178**, 17–48.

BROWN, A. G. and GORDON, G. (1977) Subcortical mechanisms concerned in somatic sensation. *British Medical Bulletin*, **33**, 121–128.

BURTON, H. and LOEWY, A. D. (1977) Projections to the spinal cord from medullary somatosensory relay nuclei. *Journal of Comparative Neurology*, **173**, 773–792.

CARPENTER, M. B., STEIN, B. M. and SHRIVER, J. E. (1968) Central projections of spinal dorsal roots in the monkey. II. Lower thoracic, lumbosacral and coccygeal dorsal roots. *American Journal of Anatomy*, **123**, 75–118.

CHANG, H. T. and RUCH, T. C. (1947) Organization of the dorsal columns of the spinal cord and their nuclei in the spider monkey. *Journal of Anatomy*, **81**, 140–149.

CHEEK, M. D., RUSTIONI, A. and TREVINO, D. L. (1975) Dorsal column nuclei projections to the cerebellar cortex in cats as revealed by the use of the retrograde transport of horseradish peroxidase. *Journal of Comparative Neurology*, **164**, 31–46.

COWAN, W. M., GOTTLIEB, D. I., HENDRICKSON, A. E., PRICE, J. L. and WOOLSEY, T. A. (1972) The autoradiographic demonstration of axonal connections in the central nervous system. *Brain Research, Amsterdam*, **37**, 21–52.

DART, A. M. and GORDON, G. (1973) Some properties of spinal connections of the cat's dorsal column nuclei which do not involve the dorsal columns. *Brain Research, Amsterdam*, **48**, 61–68.

DENNIS, S. G. and MELZACK, R. (1977) Pain-signalling systems in the dorsal and ventral spinal cord. *Pain*, **4**, 97–132.

DOSTROVSKY, J. O. and MILLAR, J. (1977) Receptive fields of gracile neurons after transection of the dorsal columns. *Experimental Neurology*, **56**, 610–621.

FERRARO, A. and BARRERA, S. E. (1935*a*) Posterior column fibers and their termination in *Macacus rhesus*. *Journal of Comparative Neurology*, **62**, 507–530.

—— —— (1935*b*) The nuclei of the posterior funiculi in the *Macacus rhesus*. An anatomical and experimental investigation. *Archives of Neurology and Psychiatry*, **33**, 262–275.

GORDON, G. and JUKES, H. G. M. (1964) Dual organization of the exteroceptive components of the cat's gracile nucleus. *Journal of Physiology, London*, **173**, 263–290.

HAND, P. and VAN WINKLE, T. (1977) The efferent connections of the feline nucleus cuneatus. *Journal of Comparative Neurology*, **171**, 83–110.

HANKER, J. S., YATES, P. E., METZ, C. and RUSTIONI, A. (1977) A new specific, sensitive and non-carcinogenic reagent for the demonstration of horseradish peroxidase. *Histochemical Journal*, **9**, 789–792.

HAYES, N. and RUSTIONI, A. (1978) Toward a reliable double-label technique for the demonstration of collateral projections of neurons: use of enzymatically inactive ^{3}H-HRP. *Anatomical Record*, **190**, 416–417.

HOPKINS, D. A. and LAWRENCE, D. L. (1975) On the absence of a rubrothalamic projection in the monkey with observations on some ascending mesencephalic projections. *Journal of Comparative Neurology*, **161**, 269–294.

JOHNSON, J. I., WELKER, W. I. and PUBOLS, B. J. Jr. (1968) Somatotopic organization of raccoon dorsal column nuclei. *Journal of Comparative Neurology*, **132**, 1–44.

KERR, F. W. L. (1975) The ventral spinothalamic tract and other ascending systems of the ventral funiculus of the spinal cord. *Journal of Comparative Neurology*, **159**, 335–356.

—— (1978) Segmental circuitry of the spinal cord and nociception. In: *Pain*, Vol. 16 of *Neurosciences Research Program Bulletin*. Edited by F. W. L. Kerr and K. L. Casey. Cambridge, Mass.: MIT Press, pp. 51–65.

KUYPERS, H. G. J. M. and TUERK, J. D. (1964) The distribution of the cortical fibres within the nuclei cuneatus and gracilis in the cat. *Journal of Anatomy*, **98**, 143–162.

LOE, P. R., WHITSEL, B. L., DREYER, D. A. and METZ, C. B. (1977) Body representation in ventrobasal thalamus of macaque: a single-unit analysis. *Journal of Neurophysiology*, **40**, 1339–1355.

MEHLER, W. R., FEFERMAN, M. E. and NAUTA, W. J. H. (1960) Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. *Brain*, **83**, 718–750.

MOFFIE, D. (1975) Spinothalamic fibers, pain conduction and cordotomy. *Clinical Neurology and Neurosurgery*, **78**, 261–268.

MOLENAAR, I. (1977) An anatomical study of the propriospinal connections in the cat. Doctoral Thesis; Rotterdam: Bronder-Offset B.V.

NIJENSOHN, D. E. and KERR, F. W. L. (1975) The ascending projections of the dorsolateral funiculus of the spinal cord in the primate. *Journal of Comparative Neurology*, **161**, 459–470.

OLSZEWSKY, J. (1952) *The Thalamus of the Macaca Mulatta. An Atlas for Use With the Stereotaxic Instrument*. Basel: Karger.

RAKIC, P. (1975) Local circuit neurons. *Neurosciences Research Program Bulletin*, **13**, 295–416.

Ramón y. Cajal, S. (1952) *Histologie du Système Nerveux*. Madrid: Consejo Superior de Investigaciones Cientificas, Vol. I, pp. 386-392.

Rastad, J., Jankowska, E. and Westman, J. (1977) Arborization of initial axon collaterals of spinocervical tract cells stained intracellularly with horseradish peroxidase. *Brain Research, Amsterdam*, **135**, 1-10.

Rexed, B. (1952) The cytoarchitectonic organization of the spinal cord in the cat. *Journal of Comparative Neurology*, **96**, 415-436.

Rustioni, A. (1973) Non-primary afferents to the nucleus gracilis from the lumbar cord of the cat. *Brain Research, Amsterdam*, **51**, 71-95.

—— (1974) Non-primary afferents to the cuneate nucleus in the brachial dorsal funiculus of the cat. *Brain Research, Amsterdam*, **75**, 247-259.

—— (1977) Spinal neurons project to the dorsal column nuclei of Rhesus monkeys. *Science*, **196**, 656-658.

—— and Kaufman, A. B. (1977) Identification of cells of origin of non-primary afferents to the dorsal column nuclei of the cat. *Experimental Brain Research*, **27**, 1-14.

—— and Macchi, G. (1968) Distribution of dorsal root fibers in the medulla oblongata of the cat. *Journal of Comparative Neurology*, **134**, 113-126.

—— and Molenaar, I. (1975) Dorsal column nuclei afferents in the lateral funiculus of the cat: distribution pattern and absence of sprouting after chronic deafferentation. *Experimental Brain Research*, **23**, 1-12.

Sadjadpour, K. and Brodal, A. (1968) The vestibular nuclei in man. A morphological study in the light of experimental findings in the cat. *Journal für Hirnforschung*, **10**, 299-323.

Shriver, J. E., Stein, B. M. and Carpenter, M. B. (1968) Central projections of spinal dorsal roots in the monkey. I. Cervical and upper thoracic dorsal roots. *American Journal of Anatomy*, **123**, 27-74.

Snow, P. J., Rose, P. K. and Brown, A. G. (1976) Tracing axons and axon collaterals of spinal neurons using intracellular injection of horseradish peroxidase. *Science*, **191**, 312-313.

Uddenberg, N. (1966) Functional organization of long, second-order afferents in the dorsal funiculus. *Experimental Brain Research*, **4**, 377-382.

Wall, P. D. and Noordenbos, W. (1977) Sensory functions which remain in man after complete transection of dorsal columns. *Brain*, **100**, 641-653.

Werner, G. and Whitsel, B. L. (1973) Functional organization of the somatosensory cortex. In: *Handbook of Sensory Physiology*. Edited by A. Iggo. Berlin: Springer-Verlag, pp. 621-700.

Whitsel, B. L., Petrucelli, L. M. and Sapiro, G. (1969) Modality representation in the lumbar and cervical fasciculus gracilis of squirrel monkey. *Brain Research, Amsterdam*, **15**, 67-78.

—— Rustioni, A., Dreyer, D. A., Loe, P. R., Allen, E. E. and Metz, C. B. (1978) Thalamic projections to S-I in macaque monkey. *Journal of Comparative Neurology*, **178**, 385-410.

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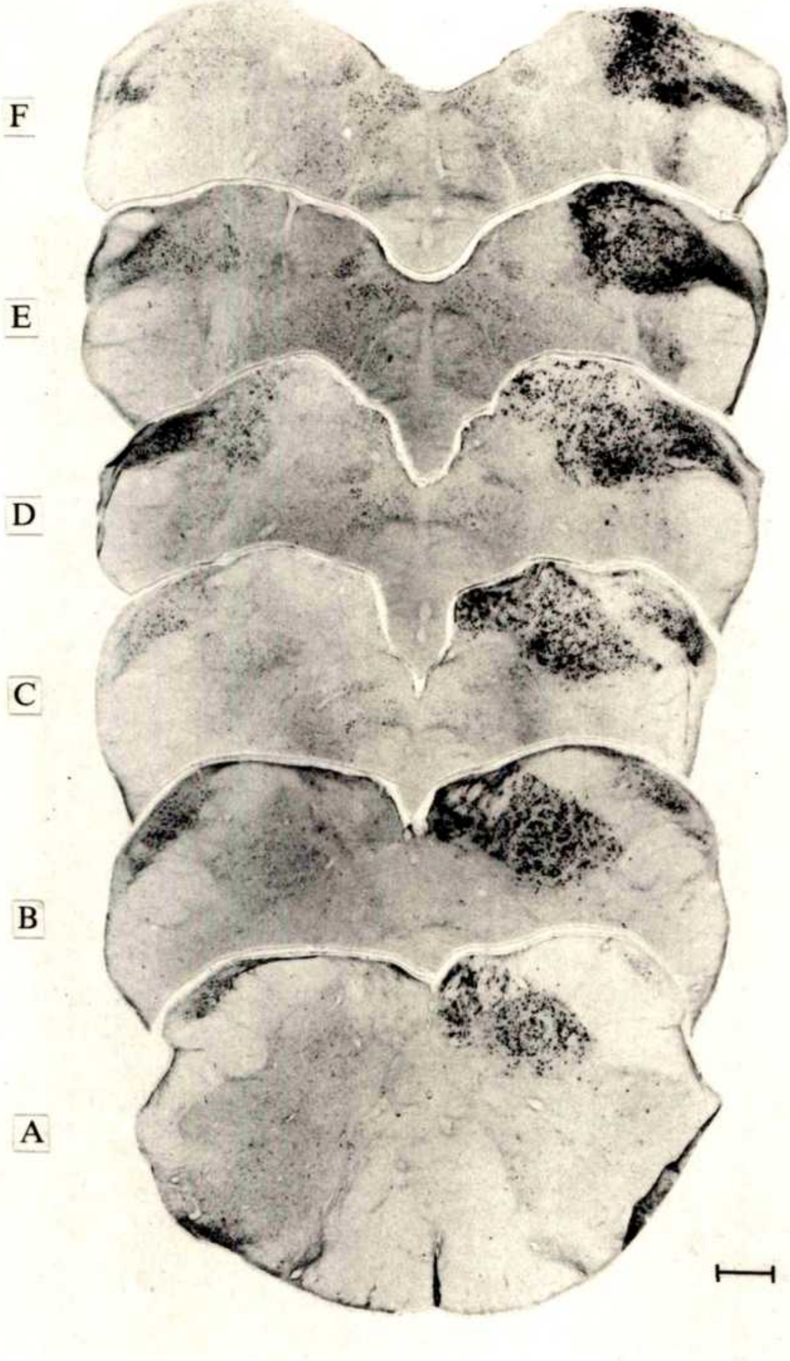

Plate I

Brain (1979), **102**, 127–146

PROXIMAL LIMB MOVEMENTS IN RESPONSE TO MICROSTIMULATION OF PRIMATE DENTATE AND INTERPOSITUS NUCLEI MEDIATED BY BRAIN-STEM STRUCTURES

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INTRODUCTION

IT has been stressed that the intermediate and lateral part of cerebellum, acting through interpositus and dentate nuclei, respectively, are concerned with planned, fine distal movements (Evarts and Thach, 1969; Allen and Tsukahara, 1974). This correlates with the evolutionary acquisition of skilled distal movements in primates paralleled by an increase of the cerebellar hemispheres (Allen and Tsukahara, 1974). Clinical data derived from stereotaxic operations on cerebellar nuclei in humans point towards a mechanism that influences posture and tonus (Tóth, 1961; Nashold and Slaughter, 1969; Siegfried, Esslen, Gretener, Ketz and Perret, 1970; Siegfried, 1971; Nádvorník, Šramka, Lisý and Svička, 1972). According to Siegfried (1971), the main indication for a stereotaxic dentatotomy is spasticity, and the primary sign after dentatotomy is a muscular hypotonia. The major effect on posture seems to be a reduction in flexor tone (Nashold and Slaughter, 1969; Nádvorník *et al.*, 1972). Stimulation of dentate and interpositus in man resulted in flexor posture (Nashold and Slaughter, 1969).

Past anatomical descriptions of dentate and interpositus nuclei projecting directly to the brain-stem (Carpenter and Stevens, 1957; Cohen, Chambers and Sprague, 1958; Mehler, Vernier and Nauta, 1958; Carpenter and Nova, 1960; Graybiel, Nauta, Lasek and Nauta, 1973) and the recent neurophysiological investigations of Bantli and Bloedel (1975, 1976) suggest a functioning pathway from the cerebellum to the spinal cord directly via the brain-stem. It is possible that this pathway may mediate the postural role of the lateral cerebellum suggested by the above-mentioned clinical studies. Using the recently developed technique of microstimulation we were able to elicit motor responses which were independent of motor cortex and red nucleus and which suggest a postural role for dentate and interpositus nuclei, mediated through the brain-stem. Partial results from dentate stimulation have been published in a preliminary report (Schultz, Montgomery and Marini, 1976).

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METHODS

Preparation

Nine adult capuchin monkeys (*Cebus apella*), weighing 1·5 to 2·5 kg, were used. They were anæsthetized with a mixture of nitrous oxide (60 per cent) and oxygen (40 per cent) with additional halothane (0·5 per cent). For surgical preparation and data collection the animals were mounted in the prone position in a stereotaxic frame. The skull overlying the left cerebellum, and in one animal on both sides, was removed. Continuous monitoring of body functions included temperature (37 to 38° C), electrocardiogram, expiratory CO_2 (3 to 4 per cent), and mean blood pressure. Whenever the blood pressure could not be maintained above 90 mmHg by infusing small amounts of metaramind, the experiments were discontinued. To support cardiac function 0·01 mg Ouabain was administered i.v. at six-hour intervals. In 8 of the 9 animals, bipolar steel electrodes (tip separation 1·5 mm) were inserted stereotaxically into the right red nucleus for antidromic activation of fibres from interpositus and dentate nuclei which terminate in or pass by this nucleus *en route* to the thalamus. After surgical preparation of the animal had been completed, gas anæsthesia was discontinued. For anæsthesia, small amounts of sodium pentothal (5 mg/kg) were administered i.v. whenever necessary. Data collection was begun not less than one hour after gas anæsthesia had been discontinued.

Microstimulation

Glass insulated tungsten microelectrodes were used (Levick, 1972). Their exposed tips were 5·5 to 7·0 μm in diameter and 25 to 35 μm in length. Tips of electrodes smaller than these were found to deteriorate with stimulation before a penetration was finished. Electrodes with larger tips did not readily isolate nuclear neurons.

Penetrations were made horizontal and parallel to the midline. The posterior and anterior portions of either nucleus as well as the area of efferent fibres anterior to the nuclei were traversed in a single electrode track. In previous studies on monkeys it had been shown that a topographical input organization exists in the anteroposterior but not in the dorsoventral axis in both nuclei (Allen, Gilbert, Marini, Schultz and Yin, 1977). The cerebellum was covered with 4 per cent agar to prevent pulsations and drying. The unitary activity of nuclear neurons was recorded by conventional amplification and display techniques. Interpositus and dentate neurons were identified by antidromic activation from red nucleus. After recording along a track, microstimulation was done with the same electrode at points spaced 0·5 mm apart and wherever a neuron had been encountered.

High frequency stimulus trains were used in order to elicit movements at relatively short latencies (Andersen, Hagan, Phillips and Powell, 1975). At five points the necessary parameters were determined. An example is shown in fig. 1 for the dentate nucleus. In A, the train duration was kept at 60 ms and the thresholds for a movement (in this case elevation of the shoulder) were determined for different frequencies. The lowest frequency for the minimum threshold of 20 μA (T) was found in this and in all other cases to be between 300 and 350 Hz. In B, the frequency was kept at 330 Hz and the train duration was varied. The shortest duration for the minimum threshold was 60 ms (20 pulses). Therefore microstimulation was carried out with trains of electrode-negative pulses of 330 Hz frequency and 0·2 ms pulse width. The applied current was measured as voltage drop across a 1 kOhm resistor. At each stimulation point the current was increased in small steps from 0 to 100 μA, and frequently up to 200 μA. Thresholds were noted whenever a movement occurred. Depending on the total time of current application later histological sections often showed small lesions at points where currents 80 to 200 μA had been used for longer series of stimulation. Lesions were not seen at locations where only 3 to 5 trains of stimuli were used with several tens of seconds interval, even with currents up to 200 μA. Thresholds in the lower current ranges were not changed afterwards at these points.

The muscle contractions were studied by visual inspection and palpation. Frequently bipolar electromyographic electrodes made from 300 μm stainless steel wire were inserted into the appropriate muscles.

Lesions

Lesions were placed in the brain at several locations in the efferent pathways which were thought possibly to mediate the observed effects of stimulation. With electrodes left at points effective for muscular contraction surgical lesions were made. Microstimulation was again done at these points and the effects and their thresholds were studied. Details of the methods will be described with the results in the appropriate sections.

Histology

At the deepest point of each penetration, and in some cases at intermediate points, an electrolytic lesion was made by passing a negative current of 20 μA for 20 s through the electrode. For further landmarks the electrodes of one or more tracks late in an experiment were left in the brain, cut shortly above the surface and left *in situ* until the brain was embedded. At the termination of the experiment, the

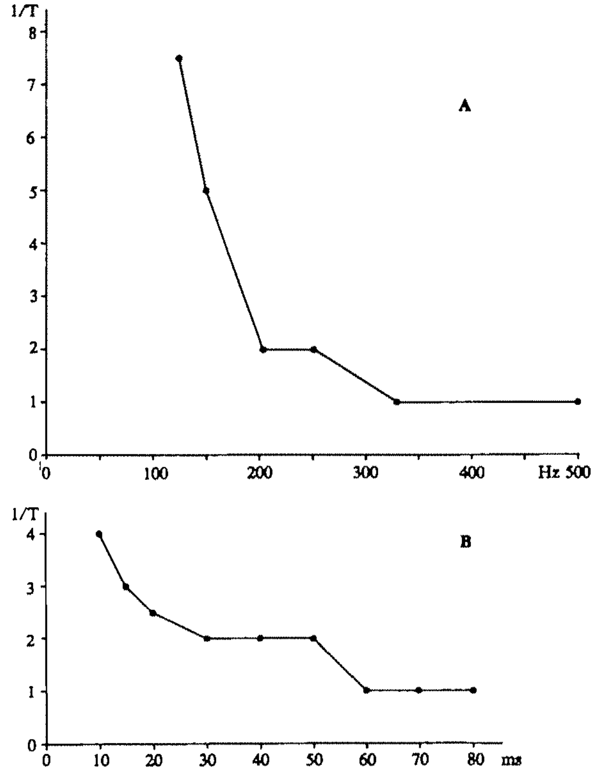

FIG. 1. Effects of different frequencies and durations of stimulus train on threshold (T) of a motor response to microstimulation of the fibre area anterior to the dentate nucleus (elevation of shoulder). A, train duration 60 ms, variation in frequency. B, frequency 330 Hz, variation in train duration. Same stimulation point in A and B. T = 20 μA.

animal was perfused with 0·9 per cent NaCl solution, followed by 10 per cent formalin. The appropriate parts of the brains were embedded in paraffin, cut in horizontal sections at 15 or 30 μm and stained with cresyl violet. The penetrations were reconstructed and the location of each stimulation site was determined. For confirming the position of the decerebration lesion, parasagittal sections of 30 μm were cut and stained according to Klüver and Barrera (1953).

RESULTS

The data were obtained from 14 electrode penetrations through dentate nucleus, 5·0 to 7·0 mm lateral to the midline and from 18 penetrations through interpositus nucleus, 2·5 to 3·8 mm lateral to the midline. All tracks were reconstructed histologically and only data obtained from points located within the nuclei or in the fibre area less than 5 mm anterior to the rostral border of either nuclei were taken into account. Eleven additional tracks that did not clearly correspond to dentate or interpositus or fibres anterior to the nuclei were not included. In the statistical analysis the only effects considered were those seen with currents up to 100 μA, applied at points at least 500 μm apart from each other to exclude effects due to spread of stimulation current (Stoney, Thompson and Asanuma, 1968; Andersen *et al.*, 1975; Bagshaw and Evans, 1976).

Character of Responses

Proximal limb movements resulted from microstimulation at 167 points that were located within or anterior to the dentate or interpositus nuclei. No responses were obtained from points in the fibre areas lateral to dentate or posterior to either nuclei as well as above the nuclei. The movements consisted of a very restricted pattern of ipsilateral proximal muscle activation. Only the following 5 movements were seen: flexion of the elbow and elevation of the shoulder in the forelimb and hip flexion, flexion of the knee and dorsiflexion of the ankle in the hindlimb. Extension movements of proximal joints were not observed after stimulation in these structures. The same manner of proximal flexor activation was seen in 4 additional tracks located in the zone of transition from dentate to interpositus, 3·8 to 5·0 mm lateral to the midline but were not included in this study. Proximal flexion or proximal extension movements were elicited from separate points in a small number of tracks that were histologically localized in the fastigial nucleus. Responses in the distal extremities occurred very rarely. Five points in interpositus and 2 points in the fibres anterior to this nucleus were effective for such movements as ipsilateral flexion or extension of fingers and flexion or adduction of toes, usually the first toe. Four of these 7 points were also effective for the proximal flexion movements already described. Conjugate deviation of the eyes to the side of stimulation was elicited from 10 points. Histological sections showed that these were located anterior to the caudal pole of dentate in the area of the midbrain tegmentum. Ipsilateral face movements were elicited from 72 points, in both nuclei and the anterior fibre areas. Sixty-three of these points were also effective for proximal flexion movements. Face and eye movements were not further investigated. Proximal limb activation was studied more closely because of the consistently limited number of movements obtained and the present report will describe only these data.

The points effective for proximal flexion movements were located along 12 tracks through dentate and 13 tracks through interpositus and the fibre areas anterior to these nuclei. Stimulation along 5 of these tracks through dentate and 4 of these tracks through interpositus were effective only in the fibre area anterior to the respective nuclei. The tracks were uniformly scattered throughout interpositus, but had a preference for the caudal part in the dentate. The 7 nonresponsive tracks and those tracks containing effective points only in the anterior fibre areas were located at the periphery of either nucleus, with one exception being situated within the interpositus.

TABLE. DISTRIBUTION OF STIMULATION SITES RESULTING IN AT LEAST ONE PROXIMAL FLEXION AND THEIR MEDIAN THRESHOLDS

	Points stimulated	*Points effective*		*Medians of threshold*
	N	*N*	%	(μA)
Interpositus	71	37	52	20
Fibres anterior to interpositus	80	69	86	27
Dentate	54	12	22	70
Fibres anterior to dentate	76	49	64	44

The percentages of stimulated points effective for one or more of the proximal flexion movements varied considerably for the two nuclei and the fibre areas anterior to them (*see* Table). Proportionately more effective points were seen in the interpositus (52 per cent) and the fibre area anterior to it (86 per cent) than in the dentate (22 per cent) and its anterior fibre area (64 per cent). The minimum amounts of current that were necessary to produce at least one movement were significantly lower in the interpositus than in the dentate ($P < 0{\cdot}001$) and also lower in the fibre area anterior to interpositus than anterior to the dentate ($P < 0{\cdot}05$, Kolmogorov-Smirnov Test (Siegel, 1956)). Thresholds were significantly lower in the fibre area anterior to the dentate as compared to the dentate itself ($P < 0{\cdot}05$), but only nonsignificant differences were seen between the interpositus and its anterior fibre area. These differences are also expressed in the corresponding medians (*see* Table). Fig. 2 shows the percentages of points effective for one or more of the 5 different movements. The number contained surpasses the total number of effective points since often more than one movement was elicited in a given threshold range. In all 4 structures more points were effective for forelimb than for hindlimb movements. Movements in the upper extremity were elicited from more than half of the stimulated points in interpositus and both fibre areas.

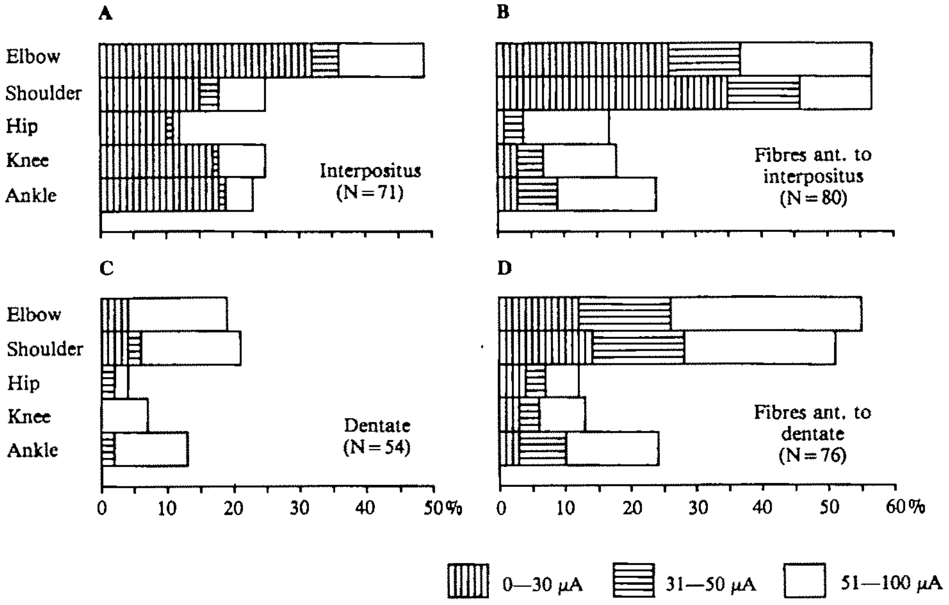

FIG. 2. Percentages of effective points for the 5 proximal limb movements in the 4 structures stimulated. Movements were: elbow flexion, elevation of the shoulder, hip flexion, knee flexion, dorsiflexion of the ankle. Responses are divided into 3 ranges according to their thresholds, as indicated. N = number of points stimulated in each structure. Often several of these movements were elicited from a given point, at same or different thresholds.

Fig. 2 also shows that stimulation with currents up to 100 μA was far less effective in producing any one of the 5 movements in the dentate nucleus than in the interpositus or the fibres anterior to either nucleus.

Responses after threshold stimulation in the dentate, interpositus or their anterior fibre areas consisted of a single flexion movement in 33 per cent and a combination of 2 to 5 individual flexion movements in 67 per cent. Frequently a combined forelimb-hindlimb movement was seen. A response consisting of at least one forelimb and one hindlimb flexion movement to a current of 100 μA was elicited from 42 per cent of all points effective for at least one proximal flexion movement. In 22 per cent of all points effective for at least one proximal flexion movement, a full pattern of at least 4 of the 5 individual flexion movements of both forelimb and hindlimb resulted. Fig. 3 shows the distribution of effective points for combined forelimb-hindlimb flexion movements for each structure.

A typical example of responses elicited when stimulating at various points along a penetration is shown in fig. 4. At the first effective point of this track through the interpositus the response was an elbow flexion and shoulder elevation with a threshold of 70 μA and a knee flexion at 80 μA. Further anteriorly ankle movements also occurred. All thresholds decreased sharply until 3·5 mm anterior to the posterior border of interpositus. Continuing rostrally the thresholds increased for nearly all movements up to the last stimulation point. This was located at the

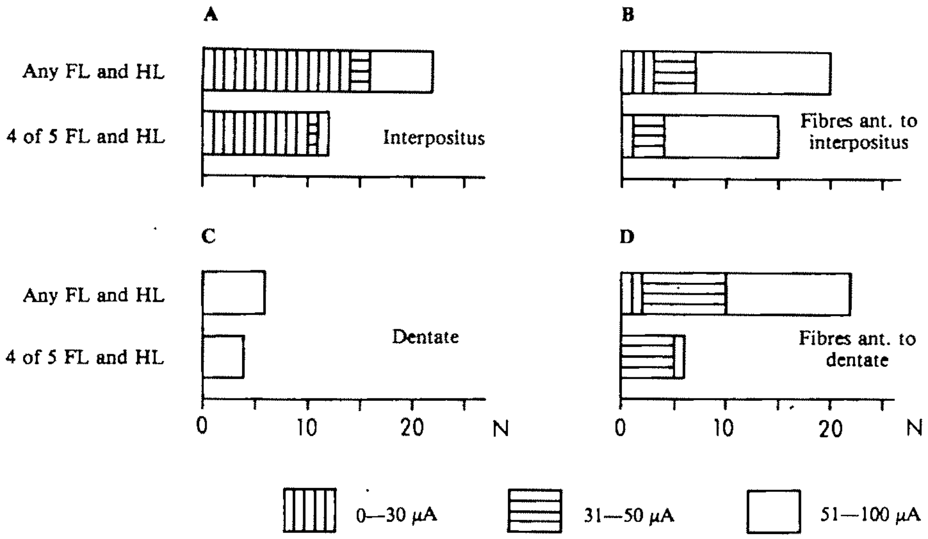

FIG. 3. Number of effective points for combined forelimb-hindlimb responses in the 4 structures stimulated. Responses consisted of combinations of the 5 forelimb (FL) and hindlimb (HL) movements described in fig. 2 and text. Three threshold ranges as indicated.

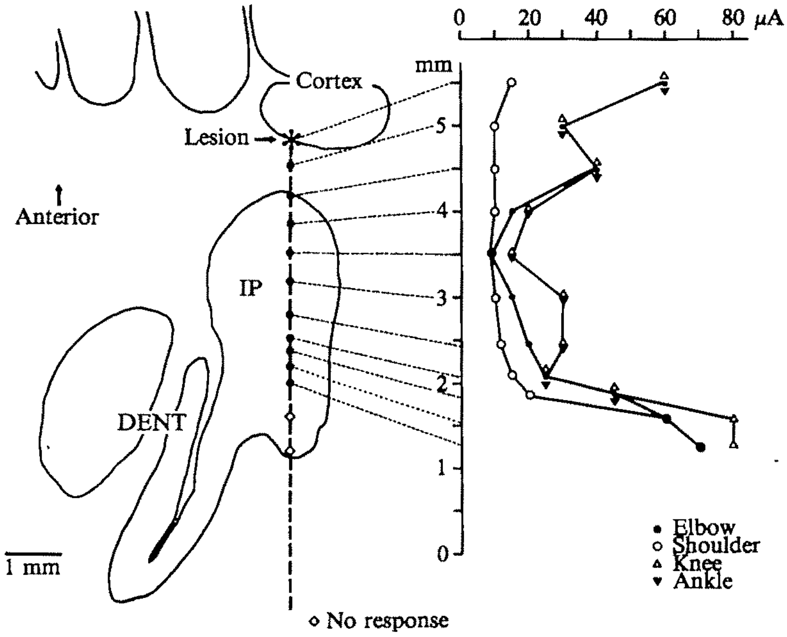

FIG. 4. Threshold ranges of different movements during stimulation along an electrode track through left interpositus (IP). Note that from any effective stimulation point more than one movement was elicited, frequently at the same threshold. Stimulation points effective for hip flexion were not encountered in this track. For description of movements *see* fig. 2 and text. Horizontal section. DENT = dentate nucleus. Star marks electrolytic lesion for identification of histological track.

border of the cerebellar cortex, where an electrolytic lesion was made after stimulation. It is evident from this figure that there was no clear difference in the thresholds between the nucleus and the area of fibres anterior to it. The thresholds tended to decrease or increase together for all movements and there was no point of minimum threshold that was particular to any movement.

No somatotopy was seen in any penetration from posterior to anterior. There occurred no systematic variation of thresholds for a particular movement or muscular activity along the dorsoventral and the mediolateral axis. This was consistent in penetrations through the dentate as well as through the interpositus.

Lesion of Motor Cortex

The primary motor cortex contralateral to the stimulation side was ablated in 4 monkeys. The electrodes were left at points effective for a typical response pattern. In 3 animals these were in the area of fibres anterior to the dentate and in one case, in the fibres anteromedial to the interpositus. The animals were more deeply anæsthetized by further i.v. injections of pentothal. With the head rigidly fixed in the head-holder, the skull and the dura overlying the contralateral motor cortex were cautiously removed. Microstimulation was repeated and the responses and thresholds were found to be largely unchanged. The motor cortex was removed by suction deep into the white matter. The shaded area of fig. 5A shows the full extent of the lesion. In all animals the lesion went medial to the depth of the callosomarginal sulcus, laterally into the sylvian fissure, anteriorly close to the superior and inferior precentral sulcus and posterior into the anterior bank of the postcentral gyrus. It included the whole of area 4 and large parts of area 6. After the lesion all responses were still present with virtually unchanged thresholds. Fig. 5A shows a typical example (the EMG is of the biceps). The response to microstimulation at a point located in the fibre area anterior to the dentate consisted of elbow flexion with 35 μA threshold, dorsiflexion of the ankle with 40 μA and knee flexion with 80 μA. After the lesion the same movements were still present and their thresholds were 40 μA for elbow flexion, 60 μA for dorsiflexion of the ankle and 80 μA for knee flexion. This demonstrates that these movements did not depend upon a pathway through the primary motor cortex.

Decerebration

Projections from dentate and interpositus nuclei to other structures include, besides area 4, the supplementary motor area (area 6), as well as parietal areas 5 and 7 (Sasaki, Matsuda and Mizuno, 1973; Rispal-Padel and Latreille, 1974; Sasaki, Kawaguchi, Oka, Sakai and Mizuno, 1976), involving ventrolateral and ventroanterior thalamic relays. Interpositus axons are also directed to the magnocellular subdivision of red nucleus (Flumerfelt, Otabe and Courville, 1973) which gives rise to the rubrospinal tract (Kuypers and Lawrence, 1967). To test the

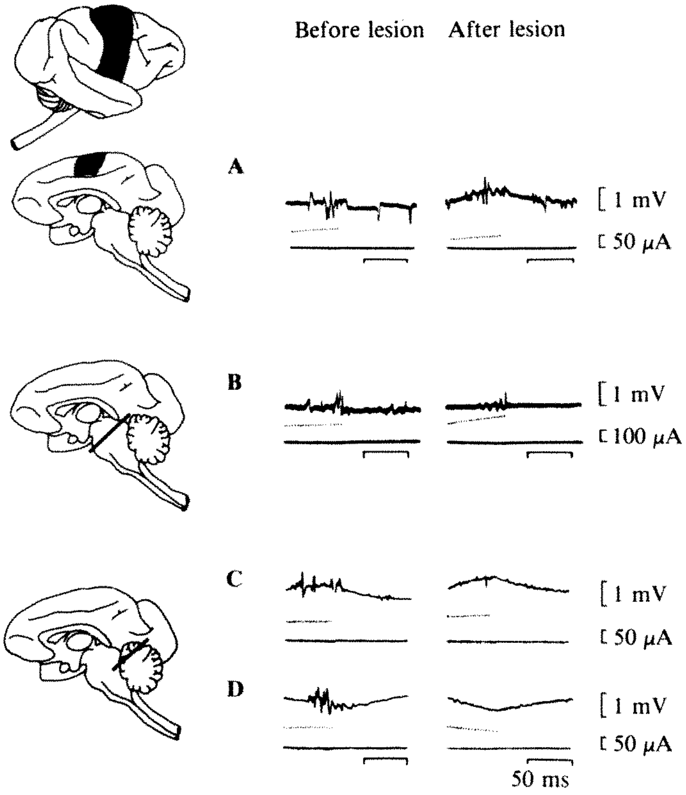

FIG. 5. Effects of lesions at different locations on the responses to microstimulation as illustrated by electromyographic (EMG) recordings. A, EMG response of biceps to microstimulation of fibres anterior to dentate nucleus before and after ablation of contralateral motor cortex. B, Effects of decerebration at a level caudal to red nucleus on EMG response of biceps. Stimulation of fibres anterior to interpositus nucleus. C, D, Effects of sectioning the brachium conjunctivum near its origin. EMGs of biceps (C) and tibialis anterior (D). Extent of decortication shown by shaded areas in A. Location of lesions indicated by bars in B and C, D. Note different scale for stimulus trace in B.

possible significance of these projections for the observed movements decerebration at the level of the colliculi was carried out in 2 monkeys. The electrodes were left at effective points in the fibre areas anterior to either nucleus. After additional administration of pentothal the occipital cortex was ablated bilaterally in order to gain access to levels anterior to the cerebellum. After removing parts of the tentorium and falx, stimulation was repeated and showed the same effects at unchanged thresholds. With a blunt spatula decerebration was performed at the level of the superior colliculus on both sides separating the forebrain completely from the brain-stem. In both monkeys the movement response to stimulation persisted after this lesion. An example is shown in fig. 5B. From a point in the fibre area anterior to the interpositus nucleus elbow flexion was elicited with 90 μA current before the lesion was performed. After the lesion the same movement was

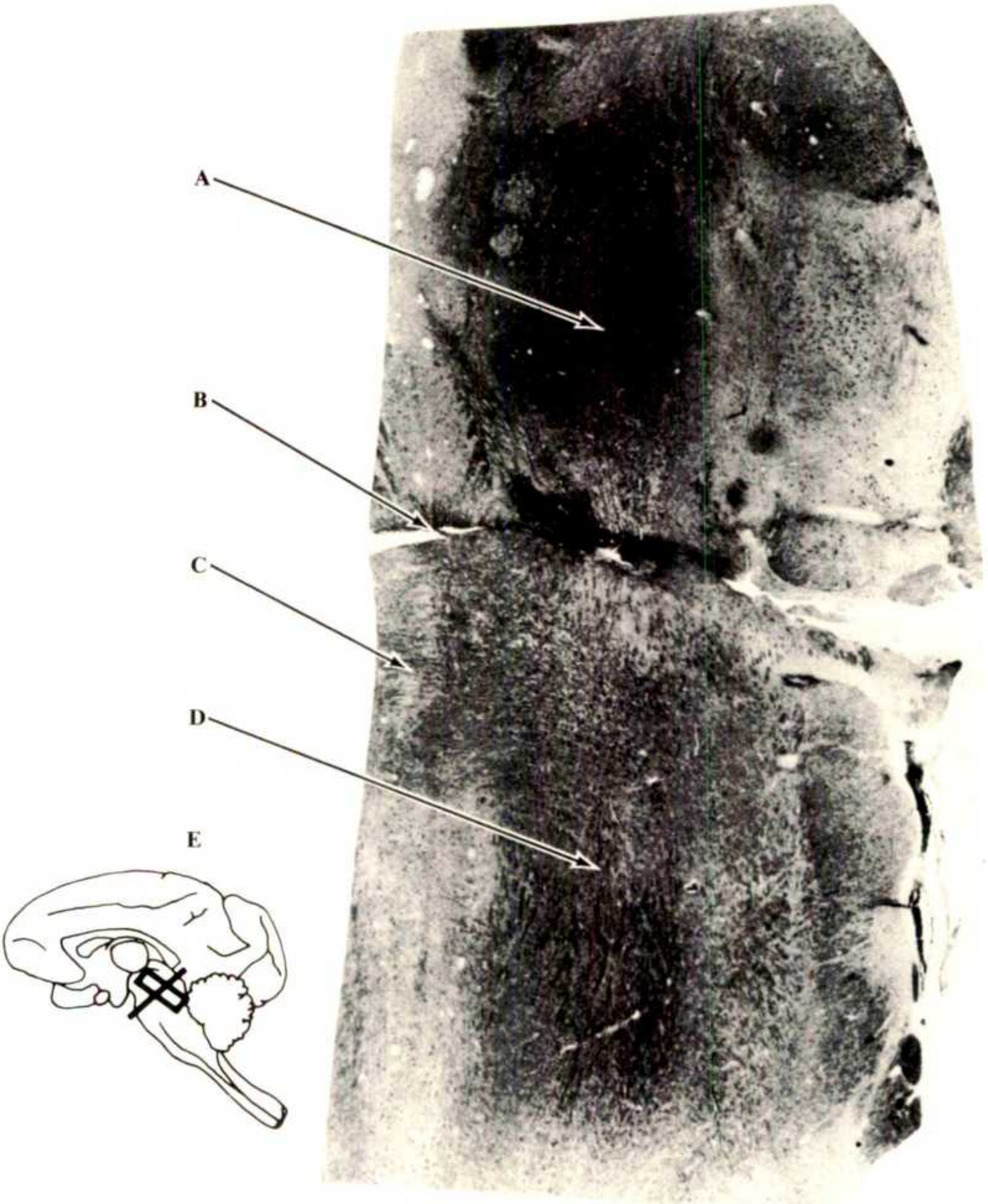

FIG. 6. Horizontal histological section of the brain-stem. A = red nucleus. B = lesion completely separating red nucleus from the decussation (C) of brachium conjunctivum (D). E = orientation of the section (represented by the rectangle) and the plane of decerebration (represented by the line through the rectangle). Klüver-Barrera stained section, 30 μm thick.

still present at the same threshold of 90 μA (the currents which evoked the EMGs of biceps shown in the figure were stronger). From a point 1 mm more posterior a combined movement of elbow flexion and shoulder elevation was elicited at 80 μA after the lesion. Fig. 6 shows a parasagittal histological section of a lesion through the brain-stem of this monkey. Figure 6E demonstrates the location and orientation of the section (shown by the rectangle) and the plane of decerebration (shown by the line through the rectangle). The lesion (B) was located posterior to the red nucleus (A) but anterior to the decussation of fibres (C) of the brachium conjunctivum (D). Obviously pathways through structures rostral to and including the red nucleus were not necessary for the movements resulting from microstimulation of the dentate, interpositus or the fibre areas anterior to these nuclei.

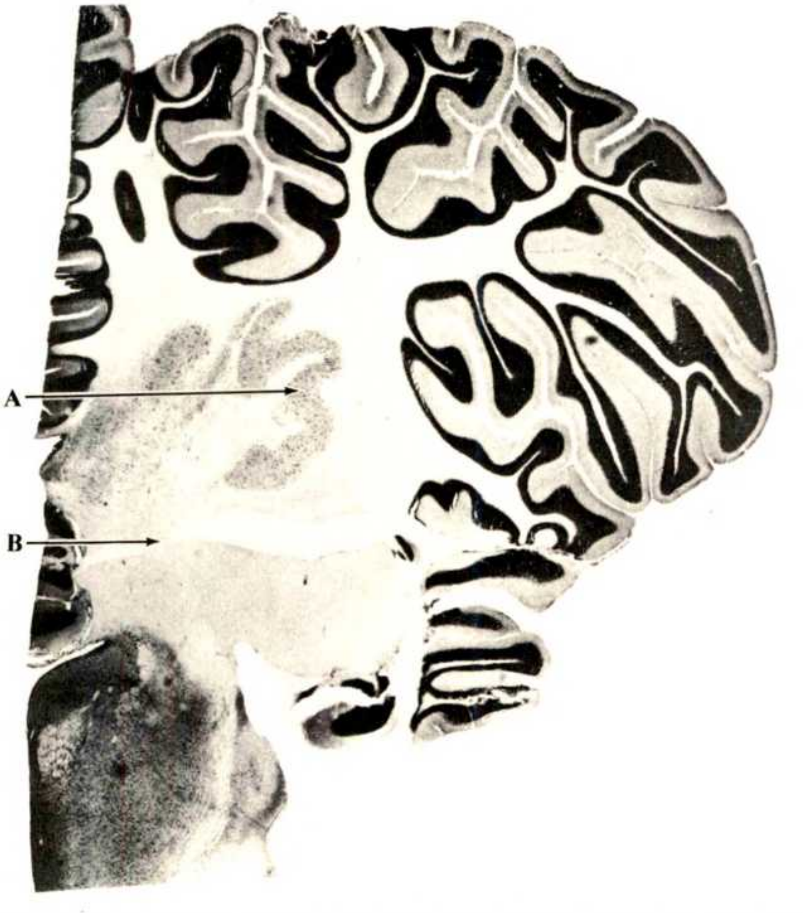

FIG. 7. Horizontal histological section of the left cerebellum showing section of the brachium conjunctivum near its origin (A = dentate nucleus, B = plane of lesion). Cresyl violet stained section, 30 μm thick.

Section of Brachium Conjunctivum

The existence of another output pathway from both nuclei was shown by Cohen, Chambers and Sprague (1958) in cats. Fibres were seen to branch off immediately after the decussation forming the descending branch of the brachium conjunctivum. In order to test whether these fibres might mediate the observed responses the brachium conjunctivum was cut between the decussation and the cerebellar nuclei in 2 monkeys. The surgical technique was the same as described for the collicular decerebration, but the lesion was made at a more caudal level. The electrode was kept in the interpositus nucleus and in the dentate fibres, respectively. After the lesion the movements were completely abolished in both monkeys. This is shown in figs. 5C, D (for biceps and tibialis anterior, respectively) for the monkey whose dentate fibre stimulation resulted in elbow flexion at a current of 30 μA, knee flexion at 40 μA and dorsiflexion of the ankle at 50 μA before the lesion. After the lesion stimulation was without effect, even with currents as high as 500 μA. The histological section showed that the lesion had separated the nuclei from the brachium conjunctivum (fig. 7). The lesion did not injure the corticospinal tract. This was demonstrated by stimulation of the white matter underlying the motor cortex, which resulted in dorsiflexion of the wrist (the white matter was exposed since decortification had been carried out on this monkey before). These results show that the motor response was only abolished by a lesion of the brachium conjunctivum near its origin involving the fibres of the descending branch.

DISCUSSION

Microstimulation

After the method of stimulation with microelectrodes had been introduced by Wall, McCulloch, Lettvin and Pitts (1956) it was considered that axons were primarily excited by this method of stimulation. This has been shown for the spinal cord, the red nucleus and the motor cortex, and in many instances presynaptic fibres appear to have the lowest thresholds (Roberts and Smith, 1973; Baldissera, Lundberg and Udo, 1972; Jankowska, Padel and Tanaka, 1975). Cell bodies do not seem to be directly activated, as originally proposed, for the motor cortex (Asanuma and Rosén, 1972), but rather trans-synaptically (Jankowska *et al.*, 1975). The character of the responses was the same with microstimulation within the nuclei as well as in the area of efferent fibres anterior to the nuclei. No responses were obtained from points above or posterior to the nuclei. This suggests that efferent axons of cerebellar nuclear neurons were responsible for the effects of stimulation, within the nuclei as well as anterior to them.

Character of Responses

Fig. 3 demonstrates that the frequency of the combined forelimb-hindlimb responses are similar in the dentate and interpositus nuclei as compared to the fibre areas anterior to these nuclei. Fig. 4 also demonstrates this point. The first point at which microstimulation was effective for any movement upon penetration of the interpositus nucleus elicited nearly the complete pattern of forelimb-hindlimb response. This would not have occurred if the explanation for the lack of somatotopy and the frequent occurrence of combined forelimb-hindlimb response was activation of more efferent fibres as the electrode penetrated more rostrally.

The experiments demonstrate a stereotyped activation of a limited number of proximal forelimb and hindlimb flexor muscles in response to microstimulation of efferent axons from the dentate and interpositus nuclei. A combined forelimb-hindlimb response was obtained in nearly half of all points that were effective for proximal movements. In nearly half of these points the full pattern of 4 of 5 individual flexion movements was seen. Distal limb movements were seen in only 7 of 281 stimulated points.

Regardless of the location of the stimulating electrode in the nuclei or fibre areas anterior to the nuclei, the response was similar. These data suggest a breakdown in efferent somatotopy. This breakdown in somatotopy need not occur at the level of the cerebellar nuclei but possibly at a more distant site in the pathway to the spinal cord.

Pathways

Ablation of the motor cortex did not alter the responses to microstimulation. This demonstrates that the responses did not depend upon the motor cortex and might suggest that the cortical output has not been effectively activated. It is unlikely that the thalamocortical relay system could transmit on a one-to-one basis the frequency used in this experiment which would be necessary to cause movement (Jankowska *et al.*, 1975; Asanuma and Rosén, 1972). An upper limit of less than 100 Hz has been shown in various sensory systems (Mountcastle, Talbot, Sakata and Hyvärinen, 1969; Hellweg, Schultz and Creutzfeldt, 1977). Also, barbiturates, as used in this study, further reduce the transmission through this route. This may occur at the level of the ventrolateral thalamus (Cohen, Housepian and Purpura, 1962; Li and Tew, 1966) and the motor cortex (Amassian and Weiner, 1966).

Brain-stem transection between the decussation of the brachium conjunctivum and red nucleus did not affect the responses to microstimulation. Sectioning of the brachium conjunctivum near its origin did abolish the response. This demonstrates that the responses in primates are mediated by the brachium conjunctivum and do not depend upon structures rostral to and including the red nucleus. This is consistent with the study of Bantli and Bloedel (1976), who reported changes in excitability of lumbar alpha motoneurons with dentate stimulation in the absence of the motor cortex. In contrast, the red nucleus was found to mediate in cats the responses to cerebellar nuclear microstimulation (Asanuma and Hunsperger, 1975) or limb hyperflexion after cerebellar ablation or cooling (Yu, 1972). The motor effects produced by microstimulation of the brachium pontis in the cat were thought to be mediated by the red nucleus (Perciavalle, Santangelo, Sapienza, Savoca and Urbano, 1977). These differences may be explained on phylogenetic grounds since the magnocellular part of the red nucleus, which gives rise to the rubrospinal tract (Kuypers and Lawrence, 1967), becomes less prominent in primates (Massion, 1967).

The brachium conjunctivum divides at its decussation into an ascending and a descending branch. In our experiments the responses were impaired only by lesions between the decussation and the cerebellar nuclei but not by lesions anterior to the decussation. This suggests that the descending branch of the brachium conjunctivum mediates the observed movements. This branch contains fibres from both dentate and interpositus in primates (Carpenter and Stevens, 1957). They project to the tegmental reticular nuclei (Cohen *et al.*, 1958; Carpenter and Nova, 1960), the medullary medial and paramedial reticular nuclei, pontine reticular nuclei (Mehler *et al.*, 1958; Carpenter and Nova, 1960) and the inferior olive (Graybiel *et al.*, 1973). Monosynaptic connections were found from interpositus to the tegmental reticular nucleus (Tsukahara and Bando, 1970; Kitai, Kocsis and Kiyohara, 1976) and from dentate to the medullary medial reticular formation (Bantli and Bloedel, 1975).

The lower pontine and medial medullary reticular formation gives rise to reticulospinal fibres (Torvik and Brodal, 1975). Monosynaptic EPSPs in motoneurons of proximal muscles were found in cats after stimulation of the reticulospinal tract (Grillner and Lund, 1966; Shapovalov, Kurchavyi, Karamjan and Repina, 1971) with the lowest threshold region located in the upper medullary medial reticular and the lower pontine reticular formation (Grillner and Lund, 1968). The EPSPs were found in motoneurons of those flexor muscles that responded in the present study. In this area electrical stimulation evoked ipsilateral facilitation of flexors and inhibition of extensors (Sprague and Chambers, 1954). This correlates very well with our experiments and strongly suggests our responses were mediated by the medullary reticular formation. The branching pattern of reticulospinal neurons would explain the nonsomatotopic character of the observed responses (Peterson, Maunz, Pitts and Màckel, 1975).

The projection from dentate to the medulla is less dense than that of the interpositus (Cohen *et al.*, 1958). This may be a factor in explaining the higher thresholds for responses with dentate microstimulation than with interpositus.

The movement responses could only be the result of activation of cerebellar efferent fibres from interpositus and dentate. It might be argued that an axonal 'reflex' could give rise to a motor response, antidromic stimulation of an afferent axon resulting in orthodromic conduction along an axon collateral. However, this is unlikely since afferent axons are not limited to the nuclei or the fibre areas anterior to them whereas effective stimulating points were. Ablation or cooling of the cerebellar cortex results in increased activity in interpositus neurons (Rosén and Scheid, 1972; Yu, Tarnecki, Chambers, Liu and Konorski, 1973) and facilitates ipsilateral forelimb and hindlimb flexion (Chambers and Sprague, 1955*a*, *b*; Yu, 1972). These results cannot be explained by an axonal 'reflex'. The activation of these nuclei and the results of ablation or cooling of the cerebellar cortex are in agreement with our experiments, confirming that our responses were the result of efferent stimulation.

The possibility that stimulating the uncinate fascicle was the cause of the responses seen in our experiments can be ruled out. Although its fibres pass in proximity or through parts of some of the stimulated structures (Rand, 1954), their course differs greatly from the location of the effective points in this study.

Postural Mechanisms

Recent theories for the role of the dentate and interpositus nuclei in voluntary movements have been proposed by Evarts and Thach (1969) and Allen and Tsukahara (1974). But the highly stereotyped activation of proximal flexors, without apparent somatotopy, which was mediated by brain-stem structures in our experiments, suggests an additional role for the dentate and interpositus nuclei in posture. The fact that the thresholds to stimulation were lower in the interpositus nucleus and the fibre area anterior to it compared to the dentate is consistent with the stronger anatomical projection of the interpositus nucleus to the brain-stem. This suggests that the interpositus nucleus may play a stronger role in postural mechanisms compared to that of the dentate nucleus. An involvement of cerebellar nuclei in postural adjustments via the cerebral cortex has previously been suggested (Massion, 1973; Rispal-Padel and Grangetto, 1977).

The effects of lesions provide additional evidence for the involvement of the dentate and interpositus in flexion posture. Coagulation of nucleus interpositus in the cat results in ipsilateral extensor hypertonus (Chambers and Sprague, 1955*a*), possibly due to loss of flexor mechanisms. Dentatectomies in man are followed by ipsilateral flexor hypotonia (Nashold and Slaughter, 1969), and relief of flexor postures (Tóth, 1961; Nádvorník *et al.*, 1972).

There is a close correlation between postural mechanisms and those structures which are involved in the central initiation of volitional movement. The inhibition of extensor (or antigravity) posture is necessary for the initiation of voluntary movement. Bard and Macht (1958) showed in their study of chronically decerebrate cats that the extensor hypertonia disappeared when the animal engaged in phasic activities. A postural role for the pyramidal systems is generally accepted (Wiesendanger, 1969) and has been investigated by Preston, Shende and Uemura (1967), who demonstrated facilitation of flexor and inhibition of extensor motoneurons with motor cortex simulation., These authors (Preston *et al.*, 1967) state that 'for the motor cortex to play a role in the initiation of volitional movements it is necessary that the tonic antigravity (extensor) postural mechanisms be arrested to permit volitional movements to occur'. These are not strictly extensor muscles that are inhibited but primarily those muscles involved in the antigravity posture.

In some specific cases where a flexor muscle is used in the antigravity posture it too is inhibited (Hore and Porter, 1972).

Similarly, in disorders of the basal ganglia a wide spectrum of abnormalities of volitional movement as well as posture may occur simultaneously (Denny-Brown, 1962). Results from single unit studies in trained monkeys suggest that the pallidum and putamen play an important role in the initiation of volitional movements (DeLong, 1971, 1973). Electrical stimulation of the caudate nucleus resulted in contralateral flexion of proximal muscles (Forman and Ward, 1957; Cools, 1973; Chandler and Crosby, 1975), and this may be mediated by brain-stem structures, as in our experiments.

The general concept is that, associated with the initiation of voluntary movement, there is a corresponding shift of postural mechanisms in favour of flexion to relieve the extensor (antigravity) posture. This function is inherent in those central structures most closely related to the initiation of voluntary movement. They include the cerebellum, the basal ganglia and the motor cortex. The results of this experiment are not inconsistent with a role of dentate and interpositus nuclei in voluntary movement but suggest that they are, in addition, involved with posture. The dentate and interpositus are involved in the initiation of voluntary movement via the ventrolateral and ventro-anterior thalamus and motor cortex and in the postural adjustments via the brain-stem, particularly the medial medullary reticular formation. It seems reasonable to apply the concept of pre-programming of voluntary movement by the dentate nucleus (Evarts and Thach, 1969; Allen and Tsukahara, 1974) to the postural adjustments necessary for the evolution of voluntary movement.

SUMMARY

The cerebellar dentate and interpositus nuclei and the area of their efferent fibres have been stimulated in Cebus monkeys, using a movable microcathode. Responses consisted of eye and face movements and a stereotyped flexion of proximal parts of extremities. Very few distal limb movements were seen. The activation of proximal muscles was studied most closely. It consisted of the limited number of 5 movements: arm flexion and shoulder elevation in the forelimb and hip flexion, knee flexion and dorsiflexion of the ankle in the hindlimb. With currents of up to 100 μA these movements were elicited more readily from the interpositus and the area of efferent fibres of both nuclei as compared to the dentate nucleus. Responses were more often seen in forelimb than in hindlimb muscles, without apparent somatotopy in either nucleus. Combined forelimb-hindlimb movements were elicited from 42 per cent of effective points. Lesions placed at various locations of cerebellar output pathways demonstrated that the responses were mediated by the descending branch of brachium conjunctivum and did not require the activation of structures anterior to and including the red nucleus. The responses are interpreted to represent adjustments in flexor posture that may serve to modify maintained

antigravity tonus during the initiation of volitional movements. This function, mediated by brain-stem structures, is considered to be closely associated with the activity of the lateral and intermediate cerebellum during initiation and conduction of volitional movements, which is mediated mainly through the cerebral cortex. It is stressed that control over both flexor posture and discrete distal movements is inherent in the initiation of voluntary movements.

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REFERENCES

ALLEN, G. I. and TSUKAHARA, N. (1974) Cerebrocerebellar communication systems. *Physiological Reviews*, **54**, 957-1006.

—— GILBERT, P. F. C., MARINI, R., SCHULTZ, W. and YIN, T. C. T. (1977) Integration of cerebral and peripheral inputs by interpositus neurons in monkey. *Experimental Brain Research*, **27**, 81-99.

AMASSIAN, V. E. and WEINER, H. (1966) Monosynaptic and polysynaptic activation of pyramidal tract neurons by thalamic stimulation. In: *The Thalamus*. Edited by D. P. Purpura and M. D. Yahr. New York and London: Columbia University Press, pp. 255-286.

ANDERSEN, P., HAGAN, P. J., PHILLIPS, C. G. and POWELL, T. P. S. (1975) Mapping by microstimulation of overlapping projections from area 4 to motor units of the baboon's hand. *Proceedings of the Royal Society B*, **188**, 31-60.

ASANUMA, H. and ROSÉN, I. (1972) Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. *Experimental Brain Research*, **14**, 243-256.

—— and HUNSPERGER, R. W. (1975) Functional significance of projection from the cerebellar nuclei to the motor cortex in the cat. *Brain Research, Amsterdam*, **98**, 73-92.

BAGSHAW, E. V. and EVANS, M. H. (1976) Measurement of current spread from microelectrodes when stimulating within the nervous system. *Experimental Brain Research*, **25**, 391-400.

BALDISSERA, F., LUNDBERG, A. and UDO, M. (1972) Stimulation of pre- and postsynaptic elements in the red nucleus. *Experimental Brain Research*, **15**, 151-167.

BANTLI, H. and BLOEDEL, J. R. (1975) Monosynaptic activation of a direct reticulospinal pathway by the dentate nucleus. *Pflügers Archiv*, **357**, 237-242.

—— —— (1976) Characteristics of the output from dentate nucleus to spinal neurons via pathways which do not involve the primary sensorimotor cortex. *Experimental Brain Research*, **25**, 199-220.

BARD, P. and MACHT, M. B. (1958) The behavior of chronically decerebrate cats. In: *Ciba Foundation Symposium on the Neurological Basis of Behavior*. Boston: Little, Brown & Co., pp. 55-75.

Carpenter, M. B. and Stevens, G. H. (1957) Structural and functional relationships between the deep cerebellar nuclei and the brachium conjunctivum in the rhesus monkey. *Journal of Comparative Neurology*, **107**, 109–163.

—— and Nova, H. R. (1960) Descending division of the brachium conjunctivum in the cat: A cerebello-reticular system. *Journal of Comparative Neurology*, **114**, 295–305.

Chambers, W. W. and Sprague, J. M. (1955*a*) Functional localization in the cerebellum: I. Organization in longitudinal cortico-nuclear zones and their contribution to the control of posture, both extrapyramidal and pyramidal. *Journal of Comparative Neurology*, **103**, 105–129.

—— —— (1955*b*) Functional localization in the cerebellum: II. Somatotopic organization in cortex and nucleus. *Archives of Neurology and Psychiatry, Chicago*, **74**, 653–680.

Chandler, W. F. and Crosby, E. C. (1975) Motor effects of stimulation and ablation of the caudate nucleus of the monkey. *Neurology, Minneapolis*, **25**, 1160–1163.

Cohen, B., Housepian, E. M. and Purpura, D. P. (1962) Intrathalamic regulation of activity in a cerebellocortical projection pathway. *Experimental Neurology*, **6**, 492–506.

Cohen, D., Chambers, W. W. and Sprague, J. M. (1958) Experimental study of the efferent projections from the cerebellar nuclei to the brainstem of the cat. *Journal of Comparative Neurology*, **109**, 233–259.

Cools, A. R. (1973) Chemical and electrical stimulation of the caudate nucleus in freely moving cats: The role of dopamine. *Brain Research, Amsterdam*, **58**, 437–451.

DeLong, M. R. (1971) Activity of pallidal neurons during movement. *Journal of Neurophysiology*, **34**, 414–427.

—— (1973) Putamen: activity of single units during slow and rapid arm movements. *Science*, **179**, 1240–1242.

Denny-Brown, D. (1962) *The Basal Ganglia and Their Relationship to Disorders of Movement*. London: Oxford University Press.

Evarts, E. V. and Thach, W. T. (1969) Motor mechanisms of the CNS: Cerebrocerebellar interrelations. *Annual Review of Physiology*, **31**, 451–498.

Flumerfelt, B. A., Otabe, S. and Courville, J. (1973) Distinct projections to the red nucleus from the dentate and interposed nuclei in the monkey. *Brain Research, Amsterdam*, **50**, 408–414.

Forman, D. and Ward, J. W. (1957) Responses to electrical stimulation of caudate nucleus in cats in chronic experiments. *Journal of Neurophysiology*, **20**, 230–244.

Graybiel, A. M., Nauta, H. J. W., Lasek, R. J. and Nauta, W. J. H. (1973) A cerebello-olivary pathway in the cat. An experimental study using autoradiographic tracing techniques. *Brain Research, Amsterdam*, **58**, 205–211.

Grillner, S. and Lund, S. (1966) A descending pathway with monosynaptic action on flexor motoneurones. *Experientia*, **22**, 390.

—— —— (1968) The origin of a descending pathway with monosynaptic action on flexor motoneurones. *Acta Physiologica Scandinavica*, **74**, 274–284.

Hellweg, F. C., Schultz, W. and Creutzfeldt, O. D. (1977) Extracellular and intracellular recordings from cat's cortical whisker projection area: thalamocortical response transformation. *Journal of Neurophysiology*, **40**, 463–479.

HORE, J. and PORTER, R. (1972) Pyramidal and extrapyramidal influences on some hindlimb motoneuron populations of the arboreal brushtailed possum (*Trichosurus vulpecula*). *Journal of Neurophysiology*, **35**, 112-121.

JANKOWSKA, E., PADEL, Y. and TANAKA, R. (1975) The mode of activation of pyramidal tract cells by intracortical stimuli. *Journal of Physiology, London*, **249**, 617-636.

KITAI, S. T., KOCSIS, J. D. and KIYOHARA, T. (1976) Electrophysiological properties of nucleus reticularis tengmenti pontis cells: Antidromic and synaptic activation. *Experimental Brain Research*, **24**, 295-309.

KLÜVER, H. and BARRERA, E. (1953) A method for the combined staining of cells and fibers in the nervous system. *Journal of Neuropathology and Experimental Neurology*, **12**, 400-403.

KUYPERS, H. and LAWRENCE, D. G. (1967) Cortical projections to the red nucleus and the brain stem in the rhesus monkey. *Brain Research, Amsterdam*, **4**, 151-188.

LEVICK, W. R. (1972) Another tungsten microelectrode. *Medical and Biological Engineering*, **10**, 510-515.

LI, C. L. and TEW, J. M. (1966) The effect of cerebellar stimulation on neuronal activity in the motor cortex. *Experimental Neurology*, **14**, 317-327.

MASSION, J. (1967) The mammalian red nucleus. *Physiological Reviews*, **47**, 383-436.

—— (1973) Intervention des voies cérébello-corticales et cortico-cerebelleuses dans l'organisation et la régulation du movement. *Journal de Physiologie, Paris*, **67**, 117A-170A.

MEHLER, W. R., VERNIER, V. G. and NAUTA, W. J. H. (1958) Efferent projections from dentate and interpositus nuclei in primates. *Anatomical Record*, **130**, 430-431.

MOUNTCASTLE, V. B., TALBOT, W. H., SAKATA, H. and HYVÄRINEN, J. (1969) Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. *Journal of Neurophysiology*, **32**, 452-484.

NÁDVORNÍK, P., ŠRAMKA, M., LISÝ, L. and SVIČKA, I. (1972) Experiences with dentatotomy. *Confinia Neurologica*, **34**, 320-324.

NASHOLD, B. S. and SLAUGHTER, D. G. (1969) Effects of stimulating or destroying the deep cerebellar regions in man. *Journal of Neurosurgery*, **31**, 172-186.

PERCIAVALLE, V., SANTANGELO, S., SAPIENZA, S., SAVOCA, F. and URBANO, A. (1977) Motor effects produced by microstimulation of brachium pontis in the cat. *Brain Research, Amsterdam*, **126**, 557-562.

PETERSON, B. W., MAUNZ, R. A., PITTS, N. G. and MACKEL, R. G. (1975) Patterns of projection and branching of reticulospinal neurons. *Experimental Brain Research*, **23**, 333-351.

PRESTON, J. B., SHENDE, M. C. and UEMURA, K. (1967) The motor cortex-pyramidal system: Patterns of facilitation and inhibition on motoneurons innervating limb musculature of cat and baboon and their possible adaptive significance. In: *Neurophysiological Basis of Normal and Abnormal Motor Activities*. Edited by M. D. Yahr, D. P. Purpura. New York: Raven Press, pp. 61-72.

RAND, R. W. (1954) An anatomical and experimental study of the cerebellar nuclei and their efferent pathways in the monkey. *Journal of Comparative Neurology*, **101**, 167-223.

RISPAL-PADEL, L. and LATREILLE, J. (1974) The organization of projections from the cerebellar nuclei to the contralateral motor cortex in the cat. *Experimental Brain Research*, **19**, 36-60.

—— and GRANGETTO, A. (1977) The cerebello-thalamocortical pathway. Topographical investigation at the unitary level in the cat. *Experimental Brain Research*, **28**, 101-123.

ROBERTS, W. J. and SMITH, D. O. (1973) Analysis of threshold currents during microstimulation of fibres in the spinal cord. *Acta Physiologica Scandinavica*, **89**, 384–394.

ROSÉN, I. and SCHEID, P. (1972) Cerebellar surface cooling influencing evoked activity in cortex and interpositus nucleus. *Brain Research, Amsterdam*, **45**, 580–584.

SASAKI, K., MATSUDA, Y. and MIZUNO, N. (1973) Distribution of cerebellar-induced responses in the cerebral cortex. *Experimental Neurology*, **39**, 342–354.

—— KAWAGUCHI, S., OKA, H., SAKAI, M. and MIZUNO, N. (1976) Electrophysiological studies on the cerebello-cerebral projections in monkeys. *Experimental Brain Research*, **24**, 495–507.

SCHULTZ, W., MONTGOMERY, E. B., Jr. and MARINI, R. (1976) Stereotyped flexion of forelimb and hindlimb to microstimulation of dentate nucleus in cebus monkeys. *Brain Research, Amsterdam*, **107**, 151–155.

SHAPOVALOV, A. I., KURCHAVYI, G. G., KARAMJAN, O. A. and REPINA, Z. A. (1971) Extrapyramidal pathways with monosynaptic effects upon primate α-motoneurons. *Experientia*, **27**, 522–524.

SIEGEL, S. (1956) *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill.

SIEGFRIED, J., ESSLEN, E., GRETENER, U., KETZ, E. and PERRET, E. (1970) Functional anatomy of the dentate nucleus in the light of stereotaxic operations. *Confinia Neurologica*, **32**, 1–10.

—— (1971) Stereotaxic cerebellar surgery. *Confinia Neurologica*, **33**, 350–360.

SPRAGUE, J. M. and CHAMBERS, W. W. (1954) Control of posture by reticular formation and cerebellum in the intact, anesthetized and unanesthetized and in the decerebrated cat. *American Journal of Physiology*, **176**, 52–64.

STONEY, S. D., Jr., THOMPSON, W. D. and ASANUMA, H. (1968) Excitation of pyramidal tract cells by intracortical microstimulation: Effective extent of stimulating current. *Journal of Neurophysiology*, **31**, 659–669.

TORVIK, A. and BRODAL, A. (1957) The origin of reticulospinal fibers in the cat. An experimental study. *Anatomical Record*, **128**, 113–135.

TÓTH, S. (1961) The effect of the removal of the nucleus dentatus on the Parkinsonian syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **24**, 143–147.

TSUKAHARA, N. and BANDO, T. (1970) Red nuclear and interposate nuclear excitation of pontine nuclear cells. *Brain Research, Amsterdam*, **19**, 295–298.

WALL, P. D., MCCULLOCH, W. S., LETTVIN, J. Y. and PITTS, W. H. (1956) The terminal arborisation of the cat's pyramidal tract determined by a new technique. *Yale Journal of Biology and Medicine*, **28**, 457–464.

WIESENDANGER, M. (1969) The pyramidal tract. Recent investigations on its morphology and function. *Ergebnisse der Physiologie, Biologischen Chemie und Experimentellen Pharmakologie*, **61**, 72–136.

YU, J. (1972) The pathway mediating ipsilateral limb hyperflexion after cerebellar paravermal cortical ablation or cooling in cats. *Experimental Neurology*, **36**, 549–562.

—— TARNECKI, R., CHAMBERS, W. W., LIU, C. N. and KONORSKI, J. (1973) Mechanisms mediating ipsilateral limb hyperflexion after cerebellar paravermal cortical ablation or cooling. *Experimental Neurology*, **38**, 144–156.

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Brain (1979), **102**, 147–161

DUCHENNE MUSCULAR DYSTROPHY

PLASMA MEMBRANE LOSS INITIATES MUSCLE CELL NECROSIS UNLESS IT IS REPAIRED

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INTRODUCTION

IN Duchenne muscular dystrophy (DMD), at least in its early and mid-phases, the main pathological sequence of events consists of repeated episodes of necrosis and regeneration of muscle cells. Though regeneration is vigorous, it does not fully compensate for necrosis. The regenerating fibres do not always attain normal size, other fibres are able to hypertrophy, and the number of muscle cells decreases. Collagen progressively accumulates in dense bundles lying between and parallel to the muscle cells, presumably as a sequel of necrosis when regeneration fails to take place.

The pathogenesis of muscle cell necrosis in DMD remains obscure. Morphological study can provide clues, if the changes which initiate necrosis could be found. This requires a clear idea of what necrosis looks like. The first purpose of this paper is therefore to provide a sequential description of the morphological features of necrosis in DMD by light and electron microscopy, with particular attention to the change which appears to initiate it, namely a breakdown of the cell membrane. A second purpose is to present evidence suggesting that small areas of plasma membrane breakdown are often repaired by the muscle cells, although, in the process, a small superficial slice of cytoplasm is lost. A third purpose is to put into proper perspective the hypercontraction which is commonly seen in biopsies of patients with DMD.

MATERIALS AND METHODS

Muscle biopsies from 30 boys with DMD were studied on cryostat and epoxy resin sections. Methods used for tissue preparation have been reported (Carpenter, Karpati, Rothman and Watters, 1976). The activity of serum creatine phosphokinase (CPK) of all patients was markedly elevated (10 to 100 times normal). All had a typical clinical picture of the disease, except for the youngest two patients (aged

9 months and 15 months), whose CPK elevation was detected by chance in a trial screening programme. They were first cousins and were regarded as having preclinical DMD. The ages of all patients range from 9 months to 10 years, with a median of 5 years. The muscles from which biopsies were taken included gastrocnemius (4), deltoid (1), and biceps brachii (25).

RESULTS

Light Microscopy

Necrosis. Necrotic muscle fibres were seen in all biopsies. A distinction was made between necrosis of muscle fibres and the phagocytosis which follows and accompanies necrosis. There was some variation in the appearance of necrotic fibres, probably because of variation in how long they had been necrotic. In some, presumably early necrotic muscle cells, most of the cytoplasm was still present. On cryostat sections stained with modified trichrome, they were paler than normal with a ground glass texture. They were rounded and somewhat swollen. Precipitated calcium was demonstrated in such cells by alizarin red S, or glyoxal bis 2-hydroxyanil stains (fig. 1). On semithin epoxy resin sections, the cytoplasm was also usually paler and more homogeneous than normal (fig. 2A, B). Some segments of necrotic muscle fibres were moderately swollen, while other segments were moderately collapsed. Z discs were not visible, though occasionally A and I bands were distinguishable on longitudinal sections. Clumps of myofibrils were sometimes at an angle to the long axis of the muscle fibre. Small dark granules (presumably mitochondria) tended to form longitudinal lines in the cytoplasm. Early macrophage invasion was represented by clusters of somewhat larger, dark, irregular

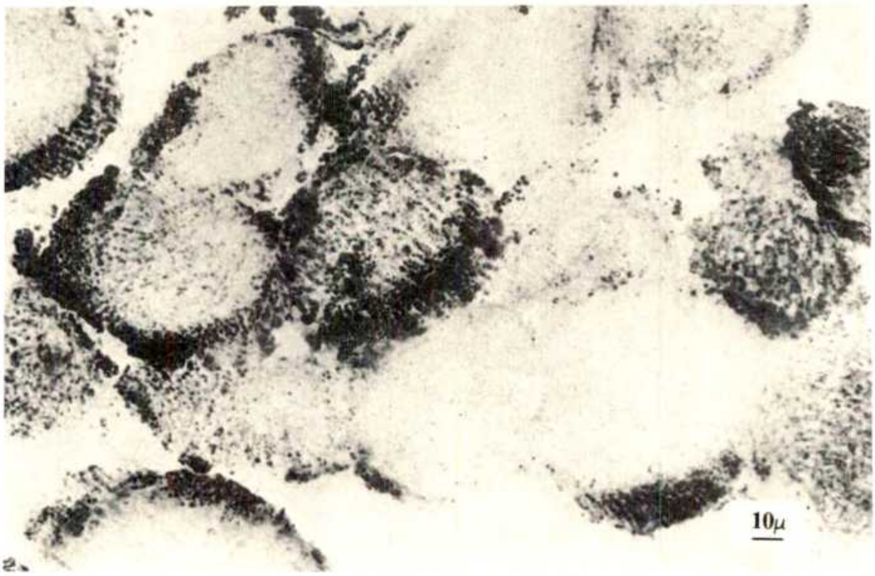

FIG. 1. Necrotic muscle fibres on transverse cryostat section show focal or diffuse punctate staining for precipitated calcium by a complexing technique, using glyoxal bis (2-hydroxyanil).

granules, usually near the cell surface (fig. 2B). Invasion by phagocytes was seen in most necrotic fibres, but the cells were distributed intermittently along the length of fibres. Nuclei of necrotic cells could not be identified; all nuclei within them appeared to belong to macrophages. Rarely, the necrotic segment of a cell seemed to be in continuity with its surviving stump, proving that necrosis was, at least sometimes, segmental (fig. 2C). We were not able to measure the longitudinal extent of necrosis in individual fibres. Most necrotic fibres were in groups although some were isolated. The largest group contained 17 necrotic fibres. On longitudinal cryostat sections, segmental necrosis in adjacent fibres ended at different points, so that a cross-section at one level would have shown an isolated necrotic fibre, and at another level, a necrotic group.

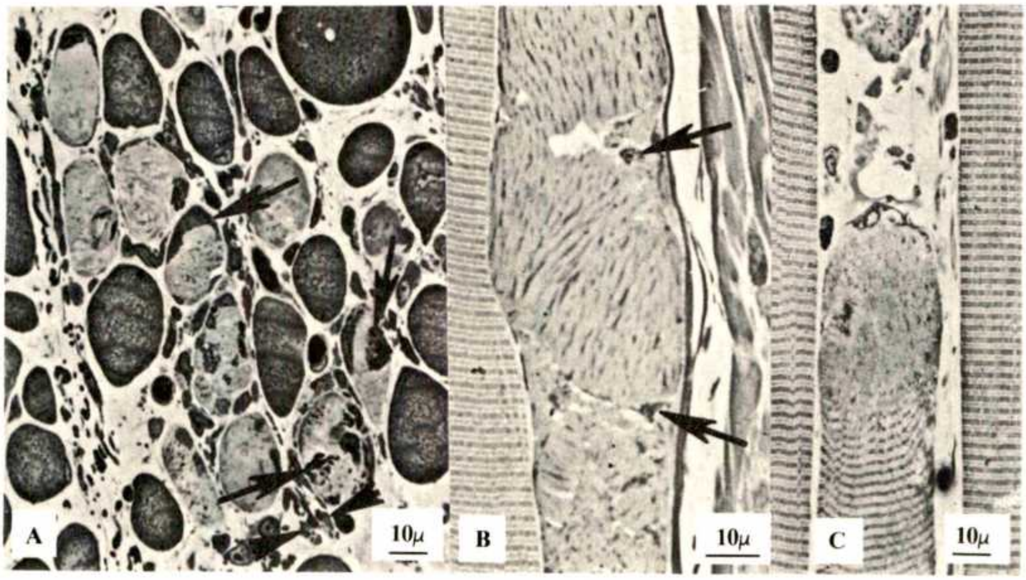

FIG. 2A, this transverse epoxy resin section shows a group of 11 necrotic fibres, which are paler than the nearby normal fibres. Phagocytes (some marked by arrows) have begun to invade the necrotic fibres. An increase of collagen in the form of discrete bundles (arrowheads) is seen in the interstitium. Paraphenylene diamine, phase optics. B, this longitudinal epoxy resin section shows a necrotic fibre in which fine dark granules (corresponding to mitochondria) are arranged in columns. Z disc is absent. Focal phagocytic invasion is indicated by groups of larger granules (arrows). A normal fibre is on the left and collagen bundles on the right. Paraphenylene diamine, phase optics. C, longitudinal epoxy resin section. The upper part of the fibre in the centre has undergone necrosis. The surviving stump on the bottom shows some disorganization of sarcomeres. Paraphenylene diamine phase optics.

Some muscle cells were filled with, or replaced by, masses of macrophages. When this occurred, the number and the outline of individual muscle cells was often difficult to make out, especially on cryostat sections. Their cross-sectional area appeared partly collapsed. The acid phosphatase reaction showed marked activity in phagocytes within necrotic cells, and to some extent in the interstitial space.

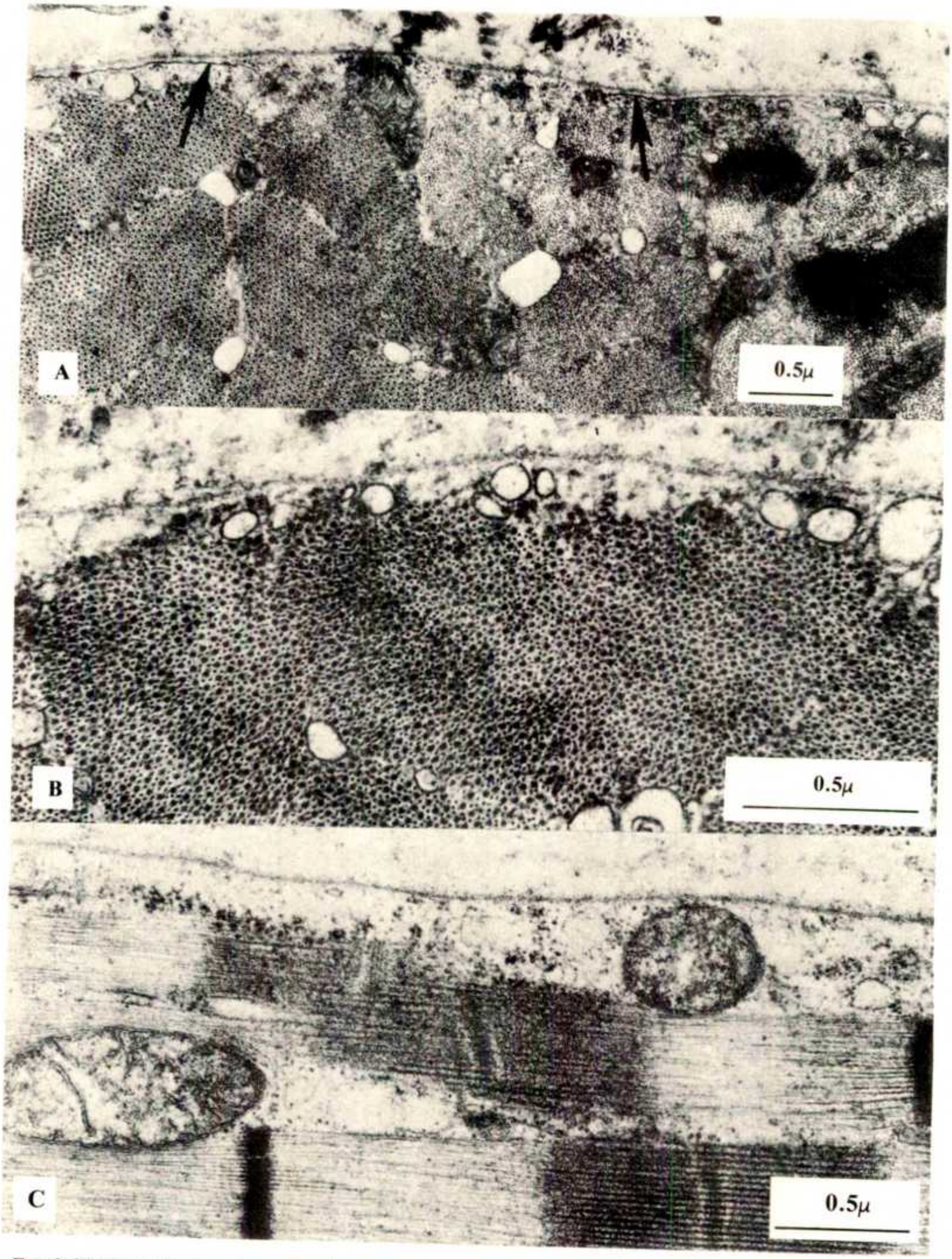

FIG. 3. Electron micrographs. A, the plasma membrane of this muscle cell is present at the left and right of the picture (arrows) but is absent in the centre. The myofilaments are in orderly arrangement and Z disc is present. Certain membrane bound spaces within the cell are abnormally dilated. B, the plasma membrane of this fibre is absent though the basal lamina persists. Subsurface vesicles are prominent. Myofibrils and mitochondria are normal. C, the plasma membrane is absent. Sarcomeres are slightly stretched.

Regenerative mononuclear myoblasts, which appear in necrotic segments during phagocytosis, could not be easily distinguished by light microscopy, while phagocytes were still present. Regenerating muscle cells, like necrotic cells, were paler than normal ones on the epoxy resin sections, but they could be identified easily by their large pale oval nuclei, with prominent nucleoli, and by the more organized appearance of the cytoplasm.

Electron Microscopy

Selective plasma membrane loss. An alteration of the plasma membrane was found in some muscle fibres from 4 biopsies from children aged 9 months, 2 years, and (two) 3 years. In these the plasma membrane was absent in part or all of the circumference of the muscle fibre (fig. 3). Tangential sectioning of the intact plasma membrane was excluded as a cause of its nonvisualization, using as criteria the crispness of the basal lamina and the closeness of organelles, such as mitochondria, to it. Complete loss of plasma membrane was part of the picture of full necrosis as described below, but the muscle fibres to which we now refer did not show other features associated with necrosis. Z discs and mitochondria were normal. The sarcomeres of such fibres were sometimes at normal resting length, or sometimes moderately overcontracted, and most were somewhat stretched apart. Within the cell there was dilatation of membrane-bound spaces (fig. 3A). When these were large their origin was not apparent; when they were small they could occasionally by their relation to lateral sacs be identified as t-tubules. In addition, vesicles were often prominent close to the surface of the muscle fibre (fig. 3B).

Fully developed necrosis. Muscle cells which were clearly necrotic were seen by electron microscopy in all biopsies (fig. 4). The plasma membrane was absent (usually over the entire circumference), but the basal lamina persisted throughout necrosis into the phase of regeneration. Mitochondria were characteristically rounded, had fluffy densities in the matrix, and linear densities in the intracristal space or outer compartment. Vesicular alteration of the mitochondrial matrix was not prominent. Z discs were invariably absent. In many necrotic cells, thick filaments were still organized into myofibrils, with recognizable M lines. Thin filaments were less well preserved but often visible. On longitudinal sections of necrotic cells, the ends of thick filaments in adjacent sarcomeres were sometimes in contact, or intermingled, while in other areas the A bands of adjacent sarcomeres were clearly separated. In other cells, myofilaments were jumbled and matted together, and myofibrillar organization was completely lost. Triads could never be seen in necrotic fibres, though vesicles might be found close to the surface. Nuclei belonging to necrotic fibres were never seen. In no case did the appearance of a necrotic fibre suggest that it had become necrotic while in the course of regeneration.

In almost all necrotic fibres, at least one phagocyte was found at some level. The cytoplasm of the phagocyte was usually relatively pale. Pseudopods encircled

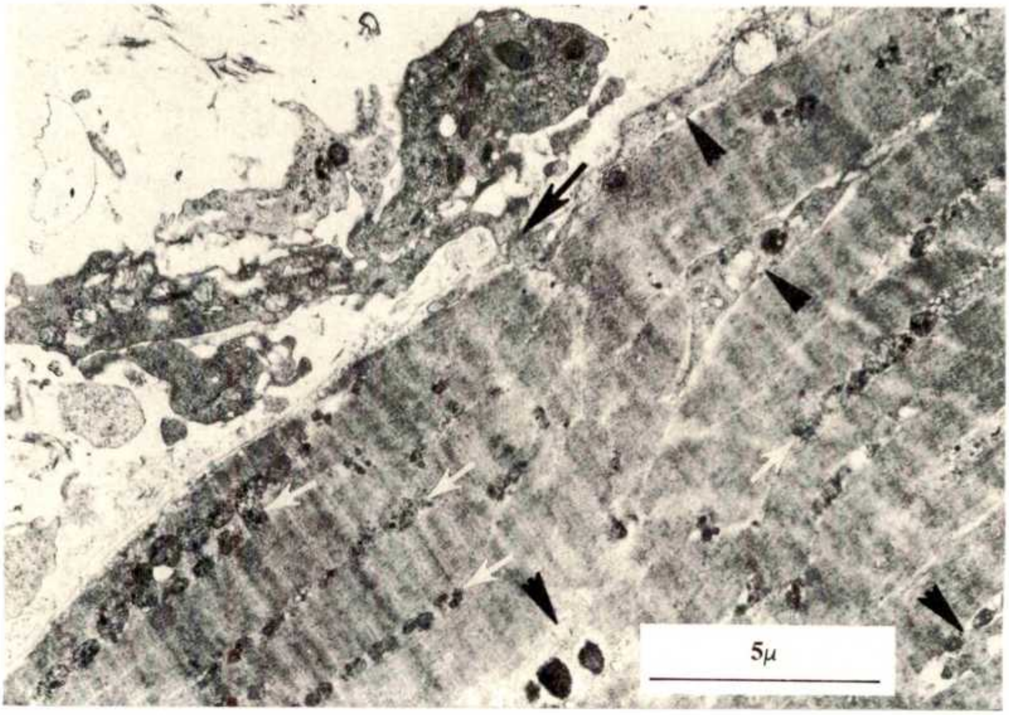

FIG. 4. Electron micrograph of a necrotic fibre. The Z disc has disappeared, though M lines are recognizable. The mitochondria are darkened and rounded and tend to accumulate in rows (white arrows). Macrophage processes, some containing lysosomes, are present in the necrotic fibre (arrowheads). A macrophage at the top of the figure is entering through the basal lamina (black arrow).

organelles or bunches of myofilaments, which, when they became completely encircled, appeared to gain in density. When phagocytosis was further advanced, the cytoplasm of the phagocytes appeared more condensed, and contained many dense bodies.

Two examples of muscle fibre stumps were seen adjacent to segmental necrosis. In one stump there was moderate disarray of myofibrils for a few microns from a membrane which demarcated the necrotic region. The other stump, which abutted on regenerative myoblasts, had orderly myofibrils up to the point of interruption (fig. 5). Abnormal mitochondria were not found in the stumps. In one muscle cell, a necrotic segment was in continuity with a non-necrotic segment, without a membrane separating them. The necrosis was advanced, since myofilaments were disorganized, and numerous macrophages were present. In the non-necrotic portions Z discs and mitochondria were intact, though marked shortening and pulling apart of sarcomeres had occurred.

Evidence of nonregeneration of individual fibres was found in some biopsies in the form of large skeins of basal lamina in the interstitial space without myoblasts or muscle cells within them (fig. 6). Many such skeins contained collagen fibrils.

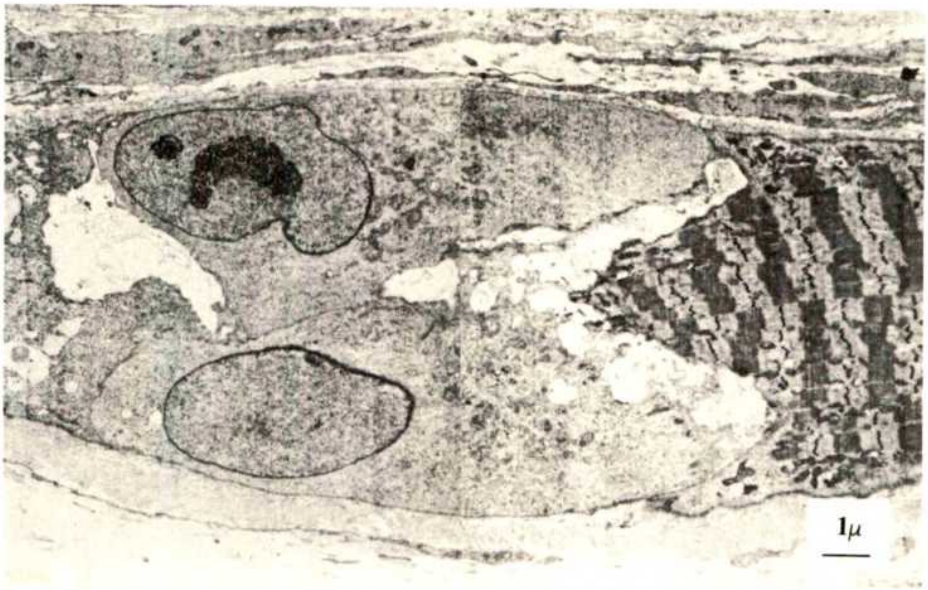

FIG. 5. This electron micrograph shows the surviving stump of a muscle fibre with two regenerative myoblasts in apposition to it. The myofibrils of the stump are in good order virtually up to the point of interruption.

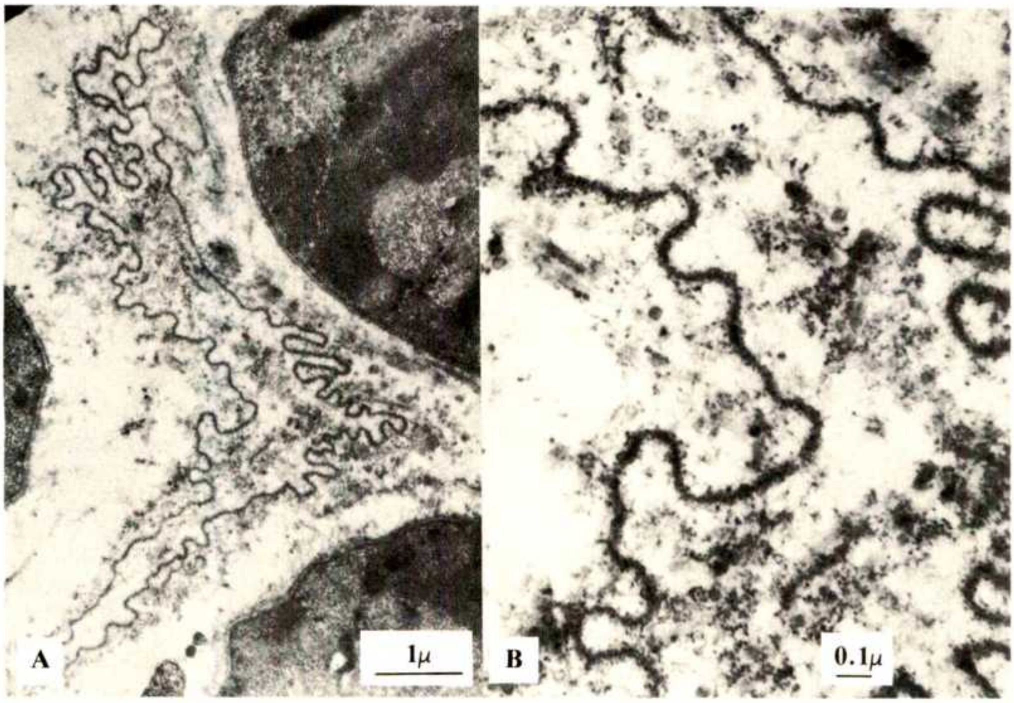

FIG. 6. A, a continuous skein of basal lamina without cellular contents lies between muscle fibres, marking the site where a muscle fibre underwent necrosis and regeneration did not follow. Collagen fibrils are present within the skein as well as next to it. B, high magnification shows collagen fibrils within the skein of basal lamina.

Apparent repair of membrane breakdown. In occasional muscle fibres of four biopsies, irregular stretches of membrane were seen running deep to the surface where the original plasma membrane was missing (fig. 7A). Between this deep membrane and the persistent basal lamina, there was a rim of cytoplasm containing

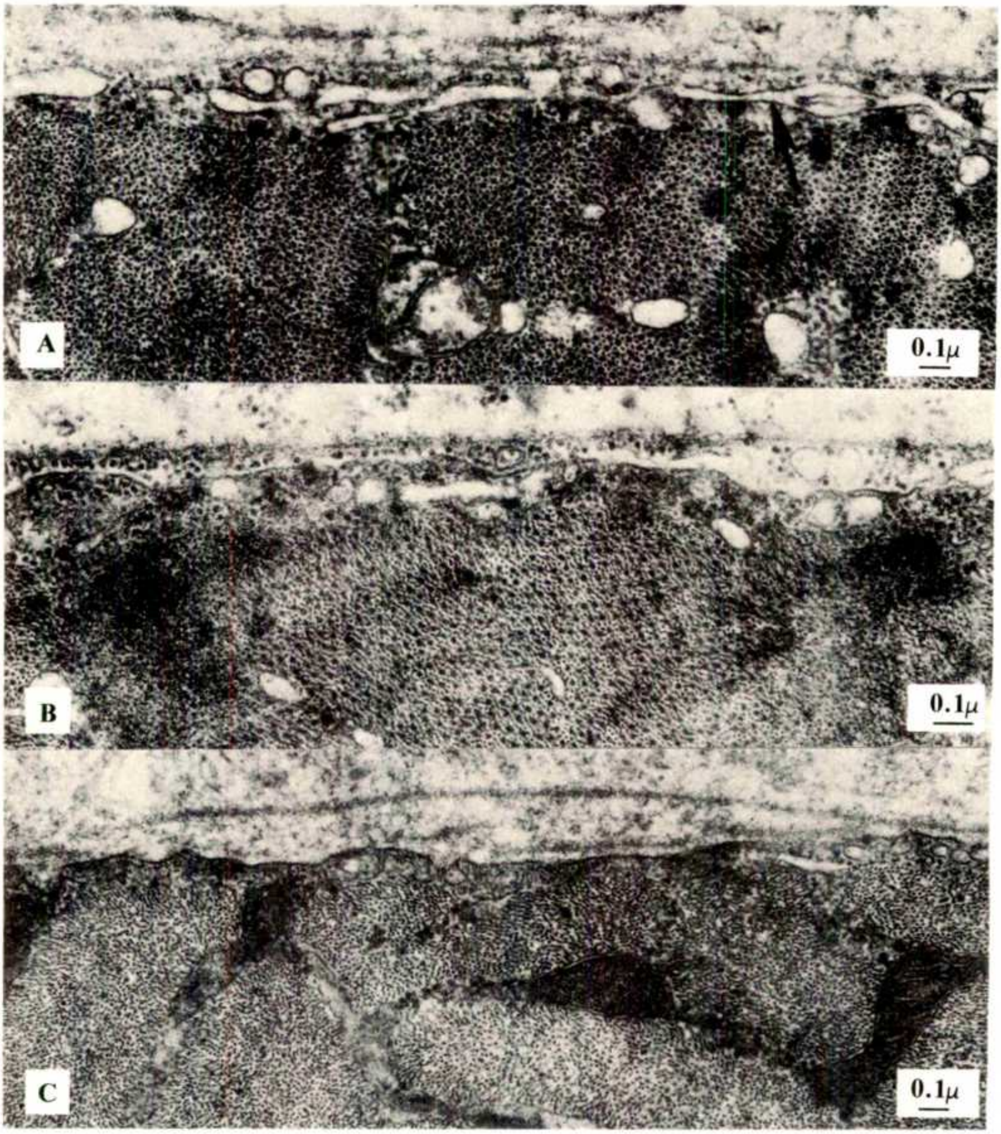

FIG. 7. A, the plasma membrane of this cell is absent but a long irregular cistern (arrow) is present beneath the surface. B, a thin slice of superficial cytoplasm containing glycogen and some vesicles is present between the basal lamina and an irregular membrane that covers the interior of the cell. This new membrane has probably been generated from a flat subsurface cistern whose outer leaf has disappeared. C, the basal lamina is separated from the surface of this muscle fibre where the surface dips down. Part of the surface is covered by a new basal lamina; part is still bare.

glycogen granules and a few vesicles. In other cells, elongated cisternal profiles stretched beneath surface membrane defects (fig. 7B). Since these cisterns were seen in both transverse and longitudinal sections, they presumably represented broad flat cisterns rather than tubules cut by chance along the lumen.

All biopsies showed muscle fibres that had pieces of lifted or reduplicated basal lamina (fig. 7C). The external leaf of this basal lamina either ended freely or was continuous at one or both ends with the basal lamina which was applied to the plasma membrane. Three or even 4 separate leaves were sometimes seen. In many instances, the reduplication began at an angulation of the plasma membrane, and extended across a slight depression in the surface of the muscle fibre. Sometimes underneath a piece of separated basal lamina, there was partial or complete lack of basal lamina next to the plasma membrane. Cell processes were sometimes found beneath the separated pieces of basal lamina. It was not clear whether these processes belonged to macrophages or to satellite cells. While reduplication of basal lamina was seen both over intact cells and necrotic cells, it was seen significantly less often over regenerating cells.

Hypercontraction. Hypercontracted fibres with extreme crowding of sarcomeres were seen in varying numbers in all biopsies. On transverse cryostat sections they appeared as enlarged round fibres that stained heavily by almost all methods. The difference between type I and type II fibres on acid pH ATPase reactions persisted despite hypercontraction. Breaks in the continuity of the muscle substance were seen in some of these fibres.

Longitudinal semithin epoxy resin sections displayed the features of hypercontraction particularly well (fig. 8A). A normal segment of muscle cell was followed by a segment in which the sarcomeres were slightly stretched and bent, so that they domed toward the next segment, where there was abrupt transition to a marked crowding of many sarcomeres. Within this segment, the individual sarcomeres were frequently not distinguishable. Next to the segment with crowded sarcomeres, there was often complete rupture of myofibrils, leaving an empty sleeve bordered by some sort of membrane. This description applies to the more tidy examples of hypercontraction, but much less tidy examples were frequently seen, in which numerous overcontracted segments were interspersed with numerous badly stretched segments, often extending only part way through the muscle fibre.

On transverse epoxy resin sections, the segments described above could also be recognized. A domed stretched segment on transverse section showed a concentric sarcomere pattern. An overcontracted segment showed as an enlarged rounded dark fibre, with a darker internal honeycomb pattern of organelles. A ruptured segment showed up as an empty oval of membrane. Hypercontracted fibres tended to be more common on the edges of biopsies than in the centre, and generally did not show much grouping.

By electron microscopy, the plasma membrane usually showed many breaks in segments where the myofibrils had ruptured and been pulled out. In segments

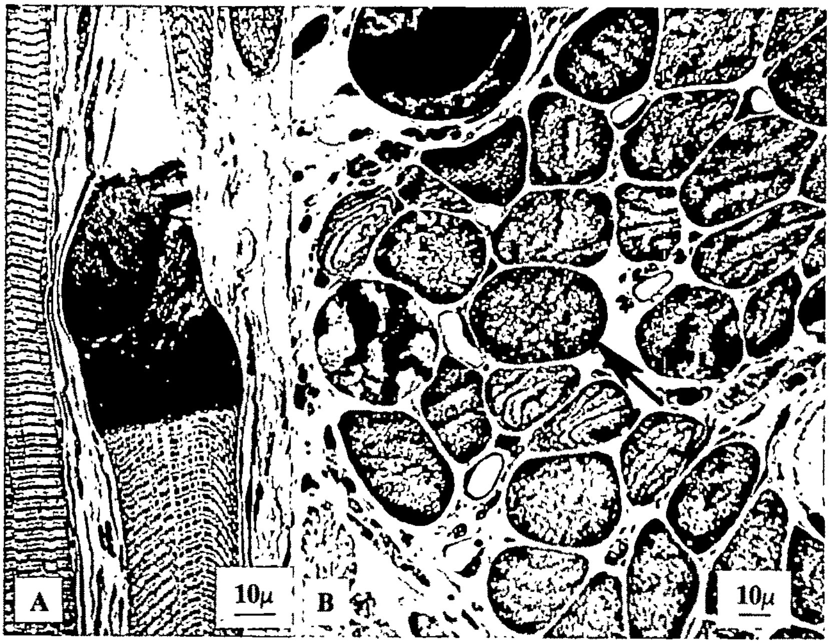

FIG. 8. A, longitudinal epoxy resin section illustrating a fibre with marked hypercontraction. In the stretched segment at the bottom the sarcomeres are domed towards the very crowded sarcomeres in the centre, while above is the empty tube from which the contents were yanked when the myofibrils ruptured. Paraphenylene diamine, phase optics. B, transverse epoxy resin section. One muscle fibre (arrow) is studded with numerous vesicles. This is the area from which the electron micrograph in figure 3B was taken. The vesicles represent dilatations of t-tubules in a fibre which has lost its plasma membrane. The appearance could be confused with that of artifactitiously swollen mitochondria such as are seen toward the centre of biopsies when the penetration of fixative has been poor. Paraphenylene diamine, phase optics.

where the myofibrils were markedly overcontracted, it was generally intact. In segments where the myofibrils were stretched, it was usually intact. Mitochondria in hypercontracted fibres did not show changes of necrosis. The Z disc, where it could be distinguished despite the crowding of sarcomeres, was present. Macrophages were never seen invading hypercontracted segments.

DISCUSSION

When we speak of necrosis, we mean that a cell, as the result of some form of injury, has entered an irreversible phase leading to the loss of all its function, as its constituents are converted to cell debris (Trump and Ginn 1969). Not all injuries lead to necrosis, and some forms of injury can cause extensive morphological alterations of cells before necrosis occurs. This is not the case in Duchenne muscular dystrophy. In necrosis, cells in general show alterations of plasma membrane and of mitochondria. In muscle cells, additional features may be expected. Disappearance of the Z disc regularly occurs early in the course of necrosis caused by a variety of injuries (Karpati, Carpenter, Melmed and Eisen, 1974; Clarke, Karpati, Carpenter and Wolfe, 1972). If the Z disc undergoes streaming before necrosis occurs, its disappearance is delayed (Karpati *et al.*, 1974). On the other hand, the contractile elements in a muscle cell can disappear without necrosis. Muscle cells can lose most of their myofibrils and still be capable of recuperation, as in childhood dermatomyositis (Carpenter, Karpati, Rothman and Watters, 1976), or after tenotomy of rat soleus muscle (Karpati, Carpenter and Eisen, 1972). We do not know how the Z disc is lysed in necrosis, but it may be mediated by a protease which normally is situated in the Z disc area, and which is activated by high calcium concentration at a neutral pH (Reville, Goll, Stromer, Robson and Dayton, 1976).

Many data suggest a membrane abnormality in DMD (Mawatari, Takagi and Rowland, 1974; Roses, Herbstreith and Appel, 1975; Mokri and Engel, 1975; Schmalbruch, 1975; Schotland, Bonilla and Van Meter, 1977). We have presented our evidence that in DMD, the first morphological reaction leading to necrosis is disappearance of the plasma membrane, since this change, always seen in the necrotic fibres, was also seen in some fibres that lacked other signs of necrosis. There must be an interval between disappearance of the plasma membrane and the other signs of necrosis, such as Z disc loss and mitochondrial alterations. The length of this interval in DMD is unknown, but it is probably quite short because it was seen only in 4 of 30 biopsies. These 4 were from some of the younger patients, in whom necrosis appeared particularly active and the chances of finding early necrotic fibres were better. In experimental ischæmia, two hours after its induction in the rat soleus, some fibres had lost Z discs completely, while in others there was partial lysis of Z discs. The later phase of full necrosis, seen in all DMD biopsies, presumably lasts much longer, probably for one or two days, and is terminated by the completion of phagocytosis. We observed that early membrane breakdown was accompanied by dilatation of membrane-bound spaces inside the fibre, some, at least, of demonstrable t-tubule origin. These dilated spaces could sometimes be seen by phase microscopy, serving as a marker of fibres with membrane loss (fig. 8B). Rather similar dilatations of the t-tubule system were produced by Girardier, Reuben, Brandt and Grundfest (1963) by various manipulations that caused acute egress of ions from sarcoplasm of crayfish muscle fibres into the t-tubules. An increased concentration of ions in the t-tubules was thought to lead to an osmotic influx of water and dilatation. In Duchenne dystrophy, in fibres which had just been denuded of their membrane, an injury current might be expected which would carry potassium ions into the t-tubule system causing osmotic influx of water and dilatation. We have noted similar dilatations in rat muscle fibres subjected to micropuncture with tungsten filaments *in vivo* (Karpati and Carpenter, unpublished observations). We did not see them in experimental ischæmia.

Phagocytosis is not *per se* a part of necrosis, but a secondary reaction to it. Phagocytosis in DMD evidently follows the onset of necrosis fairly closely, since almost all necrotic fibres had already been invaded. In experimental ischæmia, phagocytosis may not begin for several hours (Karpati *et al.*, 1974). The relative promptness in DMD probably indicates that available macrophages are present in the interstitial tissue at all times, presumably because necrosis is perenially present.

Necrosis in muscle cells differs from that in most other cells in that it may be segmental, because of the elongated nature of the cell, and the presence of multiple nuclei. This implies that the necrotic and non-necrotic segments of the cell will be in continuity until they are separated by a membrane generated by the non-necrotic segment. Examination of the stump may yield clues as to the injury which produced necrosis. In experimental ischæmia, specifically altered mitochondria are found in such stumps (Karpati *et al.*, 1974). In DMD they are not. In DMD one stump showed some disorganization of myofibrils; another did not. One example of continuity of necrotic and non-necrotic segments was seen. The non-necrotic segment showed t-tubule dilatation.

Muscle has great potential for regeneration, and in biopsies from patients with DMD regenerating fibres were numerous. Regeneration appeared to occur by the proliferation of mononuclear myoblast-like cells. That regeneration is eventually insufficient is obvious; why it is insufficient is obscure. In younger patients, puckered skeins of basal lamina without cellular contents were found in the interstitium. This appeared to represent the site of a fibre where regeneration had not followed necrosis. The cause for such nonregeneration is speculative. The residual basal lamina skein appeared to form a favourable environment for the genesis of collagen bundles, which in DMD are laid down parallel to the muscle fibres. Basement membrane bags resulting from hypercontraction with myofibrillar rupture appear different, being rounded and not containing collagen.

Plasma membrane loss in DMD was reported by Mokri and Engel (1975), who found it closely associated with subsarcolemmal areas of rarefied or absent myofibrils. We believe that these areas represent rupture of myofibrils, as the result of hypercontraction in nearby sarcomeres. The presence of marked hypercontraction in a fibre makes it impossible to tell whether adjacent plasma membrane abnormalities are simply a consequence of myofibrillar pulling and rupture. Hypercontracted fibres are frequent in biopsies from patients with DMD, but we have seen them occasionally in biopsies, especially from children, in other diseases, or in the absence of discernible disease. It is likely that hypercontraction is produced at the time of biopsy, and that it is facilitated by anything that increases the fragility of muscle fibres. In necrotic muscle fibres, various degrees of contraction of sarcomeres and buckling of myofibrils may be seen. This is not surprising in fibres whose contractile apparatus has been suddenly exposed to an extracellular environment of high calcium concentration, which can stimulate and probably dismantle the contractile apparatus. Contracted sarcomeres in necrotic fibres are generally easy to distinguish from hypercontraction, with its associated myofibrillar tears.

Schmalbruch (1975) reported loss of plasma membrane in DMD, and showed it in the absence of hypercontraction, but considered it only a prelude to hypercontraction, which he believed to be an obligatory step in necrosis. A similar theory was set forth by Cullen and Fulthorpe (1975). The organelles of hypercontracted fibres do not, however, show the changes of necrosis. The plasma membrane over hypercontracted segments is generally intact.

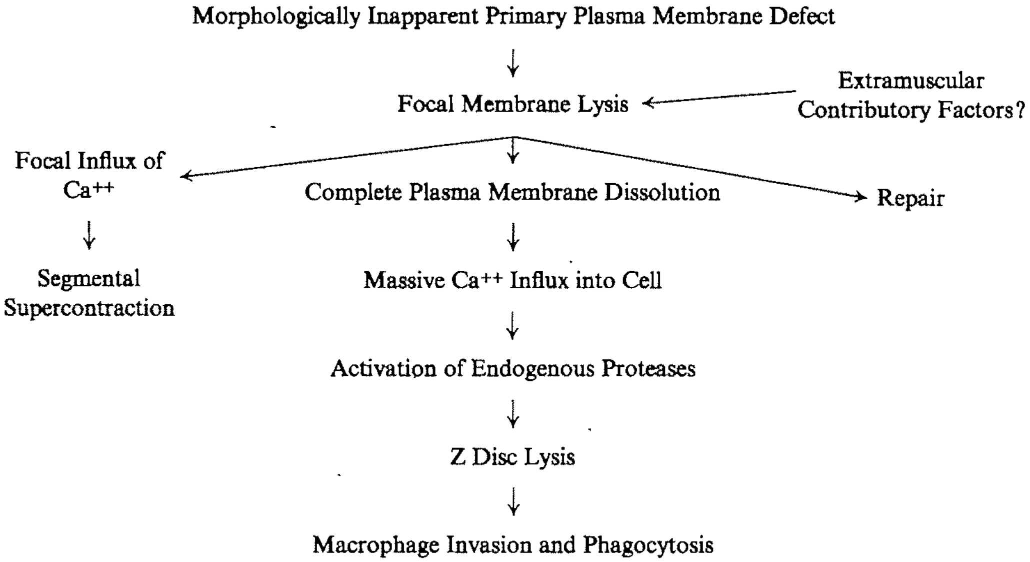
Morphologically Inapparent Primary Plasma Membrane Defect
Focal Membrane Lysis
Extramuscular Contributory Factors?
Focal Influx of Ca++
Complete Plasma Membrane Dissolution
Repair
Segmental Supercontraction
Massive Ca++ Influx into Cell
Activation of Endogenous Proteases
Z Disc Lysis
Macrophage Invasion and Phagocytosis

FIG. 9. Pathophysiology of muscle cell necrosis in Duchenne muscular dystrophy.

While large areas of membrane loss in DMD apparently must lead to necrosis, relatively small areas of loss might be repaired by a process of replacing the membrane. In some cells we found a second membrane beneath the site of the original plasma membrane. A thin layer of superficial cytoplasm was uncovered by the loss of the plasma membrane, and appeared to be disintegrating. The new membrane was apparently generated from flat cisterns accumulating beneath the uncovered area. The outer leaf of such a cistern might disappear, and the inner leaf then become the new plasma membrane. This would leave an irregular dimple in the cell surface. The original overlying basal lamina would remain separated from the new cell surface, and in time a new basal lamina would be formed next to the new cell membrane. As a result, one would expect to find pieces of reduplicated basal lamina, often overlying small depressions or irregularities in the surface of the cell. In all 30 biopsies, we found numerous such areas, presumably the residue left by previous focal membrane breakdown and repair. They were relatively rare over obviously recently regenerated fibres. It does not therefore seem possible that they could merely be sequellæ of regeneration. Examples were also seen where no new basal lamina had yet formed adjacent to the surface membrane. Lifted or reduplicated basal lamina will not, of course, be easily visible when the muscle fibres are pressed closely together. The abnormal configurations of redundant basal lamina in denervated muscle fibres are quite different.

Separation or reduplication of basal lamina, while present in all biopsies from patients with DMD, is relatively rare in other conditions. In our experience of a large series of muscle biopsies we have seen it to a minor degree in two definite carriers of DMD, in one patient with Becker dystrophy, and in hypertrophied fibres in one case of juvenile spinal muscular atrophy. Recurrent loss of portions of superficial muscle cell cytoplasm, concomitant with repair of patchy plasma membrane loss, would help to explain the increased serum CPK activity, which is characteristic of DMD, even when necrosis does not appear extensive enough to account for all of it.

Our findings permit the formulation of a working hypothesis as to the pathophysiology of muscle cell necrosis in DMD (fig. 9). Our study does not resolve the question of whether a metabolic abnormality of the plasma membrane precedes its breakdown. Such an abnormality might represent a primary expression of the gene defect, or be imparted upon the membrane from within or from without the muscle cell. Extramuscular factors may trigger the breakdown of a membrane with latent chemical abnormality. For example, anæsthesia with halothane and succinylcholine markedly augmented muscle cell damage in 3 young patients with DMD (Watters, Karpati and Kaplan, 1977).

SUMMARY

Study of biopsies from 30 boys with Duchenne muscular dystrophy suggests that necrosis of muscle cells is initiated by loss of plasma membrane, followed, after a short interval, by Z disc lysis and mitochondrial changes to constitute the picture of fully developed necrosis. Empty basal lamina tubes containing collagen indicated that regeneration may fail to occur. The tubes form a basis for collagen deposition. Evidence suggests that small patches of membrane loss can be repaired, though a slice of superficial cytoplasm is lost, and a piece of detached basal lamina results. The markedly hypercontracted fibres seen did not show features of necrosis.

ACKNOWLEDGEMENTS

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REFERENCES

Carpenter, S., Karpati, G., Rothman, S. and Watters, G. (1976) The childhood type of dermatomyositis. *Neurology, Minneapolis*, **26**, 952–962.

Clarke, J. T. R., Karpati, G., Carpenter, S. and Wolfe, L. S. (1972) The effect of vincristine on skeletal muscle in the rat. A correlative histochemical, ultrastructural and chemical study. *Journal of Neuropathology and Experimental Neurology*, **31**, 247–266.

Cullen, M. J. and Fulthorpe, J. J. (1975) Stages in fibre breakdown in Duchenne muscular dystrophy. An electron-microscopic study. *Journal of the Neurological Sciences*, **24**, 179–200.

Girardier, L., Reuben, J. P., Brandt, P. W. and Grundfest, H. (1963) Evidence for anion-permselective membrane in crayfish muscle fibers and its possible role in excitation-contraction coupling. *Journal of General Physiology*, **47**, 189–214.

Karpati, G., Carpenter, S. and Eisen, A. A. (1972) Experimental core-like lesions and nemaline rods. A correlative morphological and physiological study. *Archives of Neurology, Chicago*, **27**, 237–252.

—— —— Melmed, C. and Eisen, A. (1974) Experimental ischemic myopathy. *Journal of Neurological Sciences*, **23**, 129–161.

Mawatari, S., Takagi, A. and Rowland, L. P. (1974) Adenyl cyclase in normal and pathologic human muscle. *Archives of Neurology, Chicago*, **30**, 96–102.

Mokri, B. and Engel, A. G. (1975) Duchenne dystrophy: Electron microscopic findings pointing to a basic or early abnormality in the plasma membrane of the muscle fiber. *Neurology, Minneapolis*, **25**, 1111–1120.

Reville, W. J., Goll, D. E., Stromer, M. H., Robson, R. M. and Dayton, W. R. (1976) A Ca^{2+}-activated protease possibly involved in myofibrillar protein turnover. Subcellular localization of the protease in porcine skeletal muscle. *Journal of Cell Biology*, **70**, 1–8.

Roses, A. D., Herbstreith, M. H. and Appel, S. H. (1975) Membrane protein kinase alteration in Duchenne muscular dystrophy. *Nature, London*, **254**, 350–351.

Schmalbruch, H. (1975) Segmental fiber breakdown and defects of the plasmalemma in diseased human muscles. *Acta Neuropathologica, Berlin*, **33**, 129–141.

Schotland, D. L., Bonilla, E. and Van Meter, M. (1977) Duchenne dystrophy: Alteration in muscle plasma membrane structure. *Science*, **196**, 1005–1007.

Trump, B. F. and Ginn, F. L. (1969) The pathogenesis of subcellular reaction to lethal injury. *Methods and Achievement in Experimental Pathology*, **4**, 1–29.

Watters, G., Karpati, G. and Kaplan, B. (1977) Postanesthetic augmentation of muscle damage as a presenting sign in 3 patients with Duchenne muscular dystrophy. *Canadian Journal of Neurological Sciences*, **4**, 228.

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DEFECTIVE CARDIOVASCULAR REFLEXES AND SUPERSENSITIVITY TO SYMPATHOMIMETIC DRUGS IN AUTONOMIC FAILURE

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INTRODUCTION

CHRONIC autonomic failure leads to disabling postural hypotension as a result of defective constriction of blood vessels on standing (Johnson, Lee, Oppenheimer and Spalding, 1966; Bannister, Ardill and Fentem, 1967). It may occur in isolation (Bradbury and Eggleston, 1925) or in association with multiple system atrophy (Shy and Drager, 1960) or with Parkinsonism (Graham and Oppenheimer, 1969). Post-mortem studies have shown degeneration of sympathetic intermediolateral column cells (Bannister and Oppenheimer, 1972) but there is less certainty about the extent of the degeneration of sympathetic ganglia (Vanderhaeghan, Perier and Sternon, 1970; Schwartz, 1975) and sympathetic vascular endings (Kontos, Richardson and Norvell, 1975; Nanda, Boyle, Gillespie, Johnson and Keogh, 1977). The site or sites of the autonomic lesions are of importance not only in establishing a precise diagnosis but also because the choice of pressor drugs in attempting to treat the postural hypotension is affected by the presence of pre- or post-ganglionic degeneration (Davies, Bannister and Sever, 1978). Experimental studies have shown that in post-ganglionic degeneration there is both supersensitivity to intravenous noradrenaline (Trendelenburg, 1972) and reduced responsiveness to tyramine, the main action of which depends on the release of noradrenaline from stores at nerve terminals. Though there have been previous studies of the use of pressor drugs in patients with autonomic failure, no systematic correlation of the results has been reported in a series of patients with a detailed study of the defective cardiovascular reflexes. In this paper the responses of ten patients to noradrenaline and tyramine were compared with the site of the lesions indicated by physiological and biochemical studies.

METHODS

Patients

1. Ten patients, 6 male and 4 female, ranging in age from 43 to 67 years, all with chronic autonomic failure and significant postural hypotension, were studied and the clinical features are shown in Table 1. Seven patients had autonomic failure with multiple system atrophy, one had autonomic failure with Parkinsonism and 2 had pure autonomic failure. All the procedures had the informed consent of the patients. The patients had stopped taking any drugs at least a week before the drug infusion studies, except for Benzhexol in a dose of 2 mg t.d.s. in 4 patients (Patients 1, 2, 4 and 6). Patients 5, 9 and 10 had been on 9 alpha fluorohydrocortisone 0·1 mg daily until a week prior to the tests. Drug infusion studies were also undertaken on 2 patients (11 and 12) investigated for apparent chronic autonomic disturbances who were eventually proved not to have any organic defect.

2. The cardiovascular reflexes were studied by methods described in detail previously (Bannister, Sever and Gross, 1977) but a flexible polythene catheter (internal diameter 0·5 mm) was used for cannulation of the radial artery or brachial artery in place of needle puncture of the brachial artery. Blood pressure was recorded by transducer with a disposable 'head' and displayed on a Philips Cardiopan monitor, the modules of which also recorded cardiac beat to beat changes and breathing by nasal thermistor.

3. For the infusion studies the patients lay supine at rest and an intravenous cannula was introduced into each antecubital vein and was kept flushed with heparinized saline. The blood pressure and pulse rate were recorded from one arm at five minute intervals during an initial resting period of thirty minutes using a Bosomat II automatic blood pressure recorder (Bosch and Sohn, Fabrik Medizinischer Apparate D 7455 Jungingen). The instrument was calibrated at frequent intervals during the tests against a standard sphygmomanometer. During the infusions the recordings were made at one minute intervals. After the resting period two venous samples were withdrawn for estimation of basal noradrenaline. Tyramine solutions (10 mg base/ml) were made up in normal saline containing sodium metabisulphite. These solutions were sterilized by ultrafiltration and, for infusion studies, prior to administration diluted with saline to appropriate concentrations that would permit 60 to 500 μg tyramine/min to be infused. All injections and infusions were made into the cannula in the arm opposite to the side from which venous blood was withdrawn.

The tyramine infusion was given first to avoid any possibility of the results being affected by uptake of infused noradrenaline. In the first series of tests, tyramine solutions were given by means of a bolus. It was found however that a constant infusion of tyramine gave a comparable threshold to the bolus in 10 patients and made it more likely that the plasma noradrenaline sample reflected the peak value after the infusion. The bolus was then replaced by an infusion given by a motor-driven constant infusion pump in succession, step-wise, in 6 stages, at speeds sufficient to give doses from 60 μg to 500 μg of tyramine per minute. Each infusion was given over a period of four minutes, until a response of at least 15 mm of Hg occurred. When the infusion produced a rise of at least 10 mmHg, a sample of venous blood was withdrawn during the last thirty seconds of the infusion, for estimation of noradrenaline.

In the second series of tests, fifteen minutes after the completion of the previous study, freshly prepared solutions of noradrenaline were given by constant infusion pump in a similar manner. The doses and rates of noradrenaline were adjusted to give from 0·5 μg per minute to 15 μg per minute in 10 steps, until a pressor response greater than 15 mm occurred. The duration of the response to the pressor drugs was measured from the first raised blood pressure recording after the infusion started, to the first blood pressure recording that again reached the pre-infusion level.

TABLE 1. CLINICAL FEATURES

Patient No.	*Sex*	*Age*	*Duration of symptoms (yrs)*	*Postural hypotension*	*'Parkinsonism'*	*Pyramidal signs*	*Cerebellar signs*	*Detectable sweating*	*Impotence*	*Urinary symptoms*	*Diagnosis*
1	M	60	2	+	+	+	0	+	+	+	Autonomic failure with multiple system atrophy
2	F	55	6	+	+	+	0	+	—	+	Autonomic failure with multiple system atrophy
3	M	69	1	+	0	0	+	0	+	0	Autonomic failure with multiple system atrophy
4	F	49	2	+	+	0	0	+	—	+	Autonomic failure with multiple system atrophy
5	M	56	3	+	0	0	+	0	+	0	Autonomic failure with multiple system atrophy
6	M	60	7	+	+	+	0	+	+	+	Autonomic failure with multiple system atrophy
7	F	43	14	+	+	+	0	+	—	+	Autonomic failure with multiple system atrophy
8	M	48	2	+	+	0	0	+	+	0	Autonomic failure with Parkinsonism
9	M	67	16	+	0	0	0	+	+	0	Autonomic failure
10	F	54	2	+	0	0	0	+	—	0	Autonomic failure

+ present. 0 absent. — not relevant.

RESULTS

In all patients the presence of autonomic failure was confirmed by postural hypotension and associated defects of cardiovascular reflexes. These included lack of systolic overshoot in all patients, with impaired rate changes in phases II and IV of the Valsalva response, lack of sinus arrhythmia and lack of the pressor and pulse rate responses to stress (mental arithmetic) and drug induced hypertension as recorded in Table 2. The lack of a pressor or rate response to stress in 8 patients was confirmatory evidence of a sympathetic lesion, either central or peripheral or both. Defective sweating with a rise in central temperature was, by analogy, also taken as supporting a sympathetic central or peripheral lesion in the remaining 2 patients in whom a pressor stress response was at least partially preserved.

Lack of sinus arrhythmia was in general associated with greater defects in other cardiovascular reflexes than occurred in patients with preserved sinus arrhythmia. This pattern is in keeping with the progressive neuronal degeneration known to underlie autonomic failure. The cardiac rate changes to drug-induced hypertension consisted of the normal response of bradycardia in the 2 patients (7 and 8), with least affected cardiovascular reflexes, and no response in 4 patients. Tachycardia (marked in 2 patients), occurred in the remaining 4 patients presumably due to supersensitivity to noradrenaline of cardiac sympathetic receptors at the sino-atrial node. The resting plasma noradrenaline levels were in the low normal range or very low in all patients and rose little, if at all, on tilting the patient.

TABLE 2. CARDIOVASCULAR REFLEXES

Patient No.	*Blood pressure (recumbent)*	*Blood pressure (60° tilt)*	*Valsalva phase IV overshoot*	*Sinus arrhythmia*	*Pressor response to stress (2)*	*Tachycardia on mental arithmetic (3)*	*Tachycardia phase II valsalva (3)*	*Tachycardia on tilt 60° (3)*	*Change of pulse rate with drug induced hypertension (3) (4)*
1	160/94	106/74	0	0	+	0	+	0	+
2	117/82	63/40	0	0	0	0	−(1)	0	++
3	125/80	92/60	0	0	0	0	0	+	0
4	125/90	85/60	0	0	0	+	+	+	0
5	135/78	84/70	0	0	0	+	++	+	0
6	155/80	60/30	0	+	0	+	+	0	++
7	135/90	85/60	0	+	0	++	+++	+++	↓+
8	138/95	105/80	0	+	+	++	+	+++	↓+
9	130/90	85/60	0	0	0	0	0	0	0
10	128/80	80/45	0	0	0	+	+	+	+

(1) Valsalva impossible owing to bulbar weakness (Patient 2).

(3) Pulse rate rise less than 5 = 0,
pulse rate rise 6–15 = +,
pulse rate rise 16–25 = ++,
pulse rate rise more than 26 = +++.

(2) Systolic pressure rise 0–10 mm = 0, systolic pressure rise more than 10 mm = +.

(4) Pulse rate fall less than 5 = 0,
pulse rate fall more than 6 = ↓+,
pulse rate fall more than 15 = ↓++.

The responses to the pressor drug infusions are shown in Table 3 and fig. 1. This figure shows the change in systolic blood pressure in response to increasing doses of noradrenaline. For each patient although the dose was not expressed on a logarithmic scale the pressure response was remarkably linear. The responses fell into 3 groups:

(1) one patient (Patient 10) with pure autonomic failure had the greatest sensitivity, responding to one-tenth of the normal dose of noradrenaline and the response was prolonged from the normal duration of two to six minutes to eighteen minutes;

(2) six patients (Patients 1, 2, 3, 4, 5 and 9) had a moderately increased sensitivity, responding to one-tenth of the normal dose;

(3) the remaining 3 patients had only mild hypersensitivity, responding to up to one-fifth of the normal dose.

TABLE 3. DRUG INFUSION STUDIES AND PLASMA NORADRENALINE (PG/ML)

	Noradrenaline infusion					*Tyramine infusion*					*No infusions Noradrenaline concentrations*	
Patient No.	*Change of systolic pressure (mm/Hg)*	*Dose (µg/min)*	*Duration (min)*	*Supersensitivity (1)*	*Plasma noradrenaline (pg/ml)*	*Change of systolic pressure (mm/Hg)*	*Dose (µg/min)*	*Duration (min)*	*Supersensitivity (2)*	*Plasma noradrenaline (pg/ml)*	*At rest*	*During 60° tilt*
1	25	0·5	8	++	290	25	100	8	+	220	240	200
2	20	0·5	4	++	380	30	250	6	+	390	360	420
3	30	0·5	5	++	210	20	100	1	+	150	210	200
4	30	0·5	8	++	60	20	250	2	+	110	100	100
5	16	0·5	4	++	320	35	60	5	+	120	150	190
6	18	1	6	+	300	15	150	5	0	110	120	198
7	30	1	8	+	—	44	300	5	0	250	356	343
8	20	3·0	2	+	350	15	500	1	0	130	175	370
9	15	0·6	4	++	200	23	300	4	0	190	30	20
10	50	0·5	18	+++	290	25	150	11	++	390	240	225
11(C)	15	5	2	0	700	15	500	1	0	480	303	874
12(C)	15	4	6	0	600	15	500	2	0	500	450	788

(1) Noradrenaline infusion supersensitivity
4–10 µg/min for systolic rise of more than 15 mm. Normal 0
Less than 4 µg/min for systolic rise of more than 15 mm. +
Less than 0·5 µg/min for systolic rise of more than 15 mm. ++
Less than 0·5 µg/min for systolic rise of more than 40 mm. +++

(2) Tyramine infusion supersensitivity
More than 300 µg/min for systolic rise of more than 15 mm. Normal 0
Less than 300 µg/min for systolic rise of more than 15 mm. +
Less than 300 µg/min for systolic rise of more than 15 mm. duration longer than 10 mm. ++

— = blood sample not obtained. (C) Control (Patients 11 and 12).

Comparing these responses with the clinical features and cardiovascular reflexes two conclusions may be drawn:

(1) lack of sinus arrhythmia and hence impairment of baroreceptor reflexes was associated with more exaggerated pressor responses;

(2) in one patient (Patient 10) marked sensitivity to noradrenaline and prolongation of the response to eighteen minutes suggested the presence of a special type of peripheral denervation supersensitivity in addition to baroreceptor reflex block.

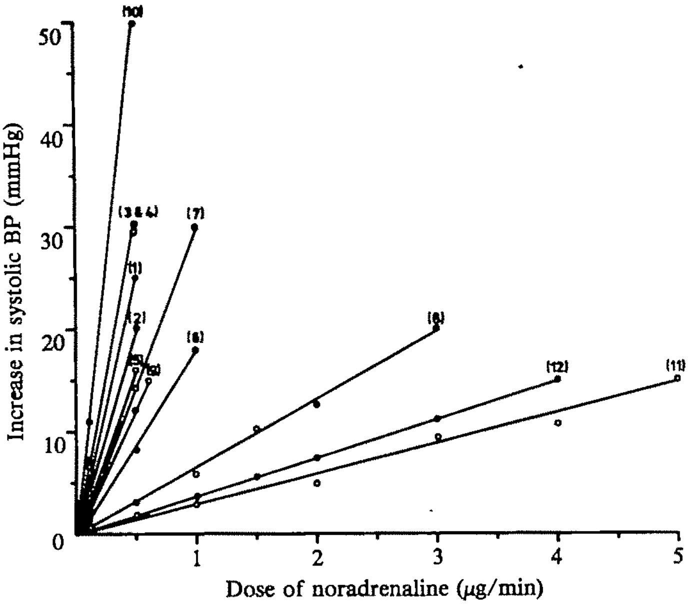

FIG. 1. A plot of the change of systolic blood pressure (BP) against the dose of intravenous noradrenaline. Numbers in parentheses above each curve indicate individual patients.

Though this patient was one of the pair with pure autonomic failure in which a distal lesion has been postulated (Kontos *et al.*, 1975; Ziegler, Lake and Kopin, 1977) she did not have a lower resting plasma noradrenaline level than the other patients.

There was no obvious correlation between the cardiovascular defects and the plasma noradrenaline at rest and after infusions of noradrenaline, except that the least affected patient (Patient 8) had a measurable rise of plasma noradrenaline after infusion and required the largest dose. In the remaining patients slight if any rise of plasma noradrenaline occurred. This is in marked contrast to the rise of some 100 per cent in the 2 control patients following a dose of noradrenaline which gave a comparable rise in systolic pressure. Patient 9 who had the lowest resting and tilt plasma noradrenaline rather surprisingly showed a rise of plasma noradrenaline after infusion.

The pressor responses to tyramine were normal or only mildly increased or prolonged with the exception of Patient 10 who had shown the exceptionally prolonged response to noradrenaline and a similarly prolonged response to tyramine. In 2 patients (9 and 10) a rise in plasma noradrenaline was detected following the infusion of tyramine, but in the remainder no significant changes were found. This contrasts with the normal subjects in whom intravenous tyramine produced an increase in plasma noradrenaline.

DISCUSSION

The interpretation of these results involves the phenomenon of supersensitivity to sympathomimetic drugs (Cannon and Rosenblueth, 1949) which is as yet incompletely understood by pharmacologists despite the advantage of studying isolated preparations following selective pre- and post-ganglionic lesions in experimental animals. A central type, called 'decentralization hypersensitivity' has been described, which is moderate in degree and relatively nonspecific and can be caused by any lesion on the proximal or pre-ganglionic sympathetic path. It is likely to be the result of reduced sympathetic impulse traffic leading to complex secondary changes in the biosynthetic enzymes altering the rate of synthesis and degradation of transmitter, in addition to changes in the integrity of the pre- and post-synaptic receptors.

The second type of supersensitivity is the 'peripheral' type, occurring after total experimental post-ganglionic section. This appears to be highly selective for sympathomimetic amines, similar to the effect of cocaine in blocking uptake or reserpine in depleting noradrenaline stores. All are associated with an increased response to noradrenaline and a reduced or absent response to tyramine (*see* fig. 2). Peripheral supersensitivity is likely to be due to a replication of the number

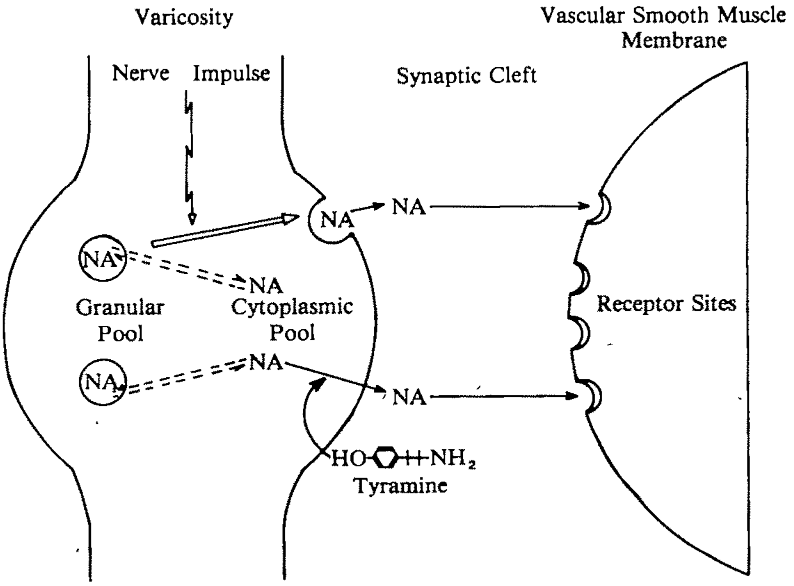

FIG. 2. Schematic representations of release of noradrenaline from a terminal varicosity on a sympathetic nerve by a nerve impulse (*upper part*) and by tyramine (*lower part*). Tyramine is taken into the nerve terminal by the active uptake process (uptake 1) which also removes noradrenaline from the synaptic cleft. Inside the varicosity it brings about release of noradrenaline which is free in the cytoplasm (cytoplasmic pool); noradrenaline found inside the granular vesicles (granular pool) cannot be released directly by tyramine. Nerve impulses, however, result in release of noradrenaline from the granular pool.
⎍⎍ effect of nerve impulse. ⇒ release of noradrenaline by fusion of vesicle with plasma membrane.
⇌ reversible equilibrium for exchange of noradrenaline between the vesicles and the cytoplasm.

of receptor sites (Trendelenberg, 1963, 1972) but the increased duration of response which we have described in one patient suggests the possibility of some reduction of the rate of clearance mechanisms for the transmitter noradrenaline. It can be seen that the distinction between the central and peripheral types of supersensitivity becomes confused because there are probably structural and functional changes at the endings in both although the primary site of the lesion differs.

Views on the site of the lesion in patients with autonomic failure have evolved considerably since Barnett and Wagner (1958) showed only a moderate pressor response to intravenous noradrenaline but a marked response to ephedrine (then thought to be an indirectly acting sympathomimetic drug) in a patient with autonomic failure attributed to a 'central' lesion. They contrasted this with the marked response to noradrenaline and slight response to ephedrine in a patient with autonomic failure due to a presumed 'peripheral' lesion. They proposed denervation supersensitivity as the explanation. Since then supersensitivity to intravenous noradrenaline in autonomic failure has been confirmed by several studies (for example, Parks, Sandison, Skinner and Whelan, 1961; Engleman, Horwitz, Mueller and Sjoerdsma, 1964; Hohl, Frame and Schatz, 1965; Chokroverty, Barron, Katz, Del Greco and Sharp, 1969; Young, Asbury, Corbett and Adams, 1975; Wilcox and Aminoff, 1976). The most complete study was by Wilcox and Aminoff (1976) who, in 7 patients with chronic autonomic failure, attempted to correlate the supersensitivity to intravenous noradrenaline with the cardiovascular reflex loss. They stressed the evidence for a post-ganglionic lesion in their cases and suggested that supersensitivity might be attributed to a reduced rate of noradrenaline clearance because of a failure of neuronal uptake. Mathias, Matthews and Spalding (1977), on the other hand, after studying a single case of autonomic failure in which the vagal baroreflex pathway appeared to be intact, as judged by bradycardia with induced hypertension, ascribed the supersensitivity to defective baroreflex sympathetic efferent pathways.

With respect to the two classical types of supersensitivity our results can be compared with the supersensitivity which has been demonstrated with other neurological lesions of precise pathology. First, with the 'central' lesion at the basal ganglia or brain-stem level occurring in idiopathic Parkinsonism a three-fold increase in sensitivity to noradrenaline has been reported, attributed to reduced 'tone' in the sympathetic nervous system (Aminoff and Wilcox, 1971).

Secondly, the focal lesion at spinal cord level causing 'decentralization' of intermediolateral column cells in tetraplegics, despite the integrity of intrinsic spinal sympathetic reflexes, causes a five-fold increase in sensitivity. Mathias *et al.* (1976) attributed this to the co-existing baroreceptor sympathetic efferent block. Thirdly, pure post-ganglionic degeneration occurs in the rare peripheral subacute autonomic neuropathies (Hopkins, Neville and Bannister, 1974; Young *et al.*, 1975; Okada, Yamashita and Suwa, 1975). In such patients supersensitivity to noradrenaline has been observed during the acute phase, with abolition of the response on recovery. There are also two other sites of lesions which may indirectly affect the response to pressor drugs. The first is baroreceptor reflex loss which may prevent correction of the rise of blood pressure due to indirectly induced vasoconstriction, by means of bradycardia or release of any residual sympathetic vasoconstrictor tone (Holton and Wood, 1965). Secondly, there may be a denervation of cardiac receptors which causes an increase in the rate or force of cardiac contraction independently of the constriction of peripheral vessels.

There was evidence of involvement of one or more of these sites in all the patients with autonomic failure (Table 4). Eight out of 10 patients had a central lesion of the brain-stem or basal ganglia which, though differing from idiopathic Parkinsonism, may have contributed in a similar way to the increased sensitivity to noradrenaline. All the patients in this study must be assumed to have had intermediolateral cell loss and hence ‘decentralization’ at spinal cord level. In 7 out of 10 of the patients baroreceptor reflexes were lost adding a third factor which, from the results analysed here, was almost certainly contributing to the supersensitivity.

The surprising fact, considering the presence of basal ganglia, brain-stem and intermediolateral column lesions, in patients with autonomic failure (Table 4) is that they do not have more supersensitivity to noradrenaline. It is possible that considerable loss of traffic in the pre-ganglionic path has only a certain upper limit of effect on post-ganglionic function and this is at a maximum level in all patients with different pre-ganglionic lesions whether due to simple Parkinsonism, tetraplegia or autonomic failure. The effect of loss of baroreflexes appears to add an extra and measurable element to the sensitivity but cannot offer more than a partial explanation for the supersensitivity.

TABLE 4. CORRELATION BETWEEN LEVELS OF LESIONS AND DRUG SUPERSENSITIVITY

	Probable sites of lesions						
				Postganglionic sympathetic nerves		*Supersensitivity*	
Patient No.	*‘Central’*	*Intermedio-lateral column cells*	*Baroreflex arc*	*Cardiac*	*Blood vessel*	*Noradrenaline*	*Tyramine*
1	+	+	+	+	+	++	+
2	+	+	+	+	+	++	+
3	+	+	+	0	+	++	+
4	+	+	+	0	+	++	+
5	+	+	+	0	+	++	+
6	+	+	0	0	+	+	0
7	+	+	0	0	+	+	0
8	+	+	0	0	+	+	0
9	0	+	+	0	+	++	0
10	0	+	+	+	++	+++	++

It is a much more difficult matter to assess the significance of any post-ganglionic sympathetic lesion. The lack of rise of plasma noradrenaline in our patients with autonomic failure after intravenous noradrenaline infusion, by comparison with the rise in the control patients, may be explained by the smaller dose of noradrenaline necessary for a comparable response and consequent reduced overspill. It cannot, however, be used to give support to the possibility that noradrenaline uptake at the endings or other sites is reduced in autonomic failure. The relevant noradrenaline concentration is of course that at the synaptic cleft rather than in the venous blood (Sever and Gordon, 1978). The excessive response to infused noradrenaline in autonomic failure may be due to an increase in the number of receptors, each responding in a more or less normal manner, hence giving a normal duration of response but of excessive degree. In Case 10 however, the greatly prolonged response requires a different explanation, such as abnormal properties of the receptors or defective clearance of noradrenaline from the receptor sites and hence prolonged action. Though some degree of 'peripheral' abnormality, either of the noradrenaline content or release from the endings or an abnormality of the receptors occurred in all patients (*see* Table 4), this was clearly of a different character in Case 10. Supersensitivity in autonomic failure cannot be fully equated with the classical 'decentralization' or 'peripheral' types observed experimentally with single lesions. The whole sympathetic pathway appears to be abnormal.

In what way do the results of the tyramine infusions extend these conclusions? Responses to intravenous tyramine in autonomic failure have been studied previously by Ibrahim (1975) who, using the bolus technique, showed a range of systolic blood pressure rises from 2 to 56 mm after a 2 mg bolus. Demanet (1976) found that the pressor responses to intravenous tyramine infusion in chronic autonomic failure lay within the range of those of normal subjects. Our own results confirm this and suggest that a differential response with supersensitivity to noradrenaline and total loss of response to tyramine might only be expected if the post-ganglionic lesion were total, which does not appear to be the case in this disease.

Tyramine not only stimulates noradrenaline release (Chidsey, Harrison and Braunwald, 1962; Smith, 1973 and fig. 2) but also inhibits re-uptake into sympathetic nerves (Trendelenberg, 1962) and may also undergo metabolism to octopamine (norsynephrine) and thence to noradrenaline (Creveling, Levitt and Undenfriend, 1962; Carlsson and Waldeck, 1963). The rise of plasma noradrenaline after tyramine infusion in our 2 control patients indicates some overspill from the synaptic cleft to the venous system. The situation is clearly more complex and difficult to interpret in the patients with autonomic failure. The presence of an apparently normal or near normal response to tyramine implies some releasable noradrenaline but the lack of a rise in plasma noradrenaline (except in Patients 9 and 10), by comparison with the normal subjects, suggests that it is insufficient for the normal overspill to occur. It seems probable that there is release of only small amounts of noradrenaline from abnormal endings, but supersensitivity of the receptors.

The 2 patients, Cases 9 and 10, with pure autonomic failure have to be considered separately. In both the plasma noradrenaline did rise after tyramine infusion and it is probable that the defect in these 2 patients' sympathetic endings was different from the majority of cases with autonomic failure and more obvious central lesions. In Patient 9, in whom the recumbent tilt values of noradrenaline were immeasurably low, there may have been a defect of release, or less noradrenaline available for release by nerve impulses but not necessarily by tyramine (*see* fig. 2). Patient 10 may have had a different type of peripheral disturbance in which the defect of release was less severe so that the plasma noradrenaline was more nearly normal and the noradrenaline in the nerve ending was accessible to tyramine. The prolonged response, however, implies a defect of transmitter re-uptake or metabolism.

These results give a little support for the view that a distinction can sometimes be made on physiological and biochemical grounds between pure autonomic failure and autonomic failure with multiple system atrophy, as Ziegler *et al.* (1977) have suggested, but the same sites of autonomic degeneration are likely to be involved in varying degrees, at least from the spinal cord to the periphery. The autonomic failure may have progressed further in cases of chronic pure autonomic failure because of better tolerance of postural symptoms in the absence of Parkinsonism or other central neurological defects. Further progress in interpreting these responses may follow the use of direct arterial infusion studies of pressor drugs, measuring forearm or hand blood flow (Parks *et al.*, 1961; Bannister *et al.*, 1969) or the use of biopsy techniques to show the histochemical fluorescence of catecholamines in sympathetic vascular endings in muscle, first reported by Kontos *et al.* (1975).

What is the place of pressor drugs studies in the management of autonomic failure? Though in theory the use of noradrenaline and tyramine, which have different actions on sympathetic endings, might throw some light on the problem of siting of the lesion, limitations still exist both because lesions are partial, not complete, and because of the difficulty in deciding whether there is a single lesion on an autonomic pathway, because a primary lesion may be followed by secondary distal or central changes. There is, however, good reason to add pressor drugs to the existing tests for assessing the site of the lesion on the autonomic reflex arc (Johnson and Spalding, 1974). In terms of diagnosis, bradycardia after the elevation of blood pressure by a pressor drug provides the only direct evidence of persistence of the baroreceptor reflex arc. Tachycardia provides the only evidence of denervation supersensitivity of cardiac receptors which may be of prognostic importance in that patients with autonomic failure are at risk of sudden death, possibly due to cardiac arrhythmias. In terms of treatment, prior to the use of oral pressor drugs as therapy, there is no way other than by drug infusions to exclude the type of extreme supersensitivity which was unexpectedly found in one patient in whom the use of pressor drugs could well have caused very severe recumbent hypertension and even cerebral hæmorrhage (Davies *et al.*, 1978).

SUMMARY

In 10 patients with chronic autonomic failure the clinical features and cardiovascular reflexes were correlated with the pressor responses to intravenous noradrenaline and tyramine. In all patients there was an exaggerated response to noradrenaline but a normal or only mildly exaggerated response to tyramine. Patients with lack of sinus arrhythmia and by implication baroreceptor reflex loss had greater responsiveness to pressor drugs than patients with preservation of this reflex. The responses to tyramine infusions imply that there must be sufficient noradrenaline released at defective sympathetic endings for a pressor response to occur. However, the lack of rise of plasma noradrenaline following tyramine, except in the patients with pure autonomic failure, clearly separates these responses from those of normal subjects.

These results can be explained by the presence of lesions of both central and peripheral sympathetic pathways in patients with chronic autonomic failure and multiple system atrophy or Parkinsonism. The peripheral lesion, which is incomplete, may consist of replication of the receptors so causing supersensitivity with a duration of response that is little prolonged. The peripheral defect in the two patients with pure autonomic failure was found to be more complex and the prolonged response in one of these patients suggests the possibility of defective re-uptake or metabolism of noradrenaline. Clearly further study of the defects of sympathetic endings is required, including the use of other techniques such as catecholamine fluorescence.

The extreme supersensitive responses underline the need for blood pressure monitoring during pressor drug studies prior to treatment, if the hazards of recumbent hypertension are to be avoided.

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REFERENCES

AMINOFF, M. J. and WILCOX, C. S. (1971) Assessment of autonomic function in patients with a Parkinsonian syndrome. *British Medical Journal*, **4**, 80–84.

BANNISTER, R., ARDILL, L. and FENTEM, P. (1967) Defective autonomic control of blood vessels in idiopathic orthostatic hypotension. *Brain*, **90**, 725–746.

—— —— —— (1969) An assessment of various methods of treatment of idiopathic orthostatic hypotension. *Quarterly Journal of Medicine*, **38**, 377–395.

BANNISTER, R. and OPPENHEIMER, D. R. (1972) Degenerative diseases of the nervous system associated with autonomic failure. *Brain*, **95**, 457–474.

—— SEVER, P. and GROSS, M. (1977) Cardiovascular reflexes and biochemical responses in progressive autonomic failure. *Brain*, **100**, 327–344.

BARNETT, A. J. and WAGNER, G. R. (1958) Severe orthostatic hypotension: case report and description of response to sympatheticomimetic drugs. *American Heart Journal*, **56**, 412–424.

BRADBURY, S. and EGGLESTON, C. (1925) Postural hypotension: an autopsy upon a case. *American Heart Journal*, **1**, 73–86.

CANNON, W. B. and ROSENBLUETH, A. (1949) *The Supersensitivity of Denervated Structures: a Law of Denervation*. New York: Macmillan, p. 1.

CARLSSON, A. and WALDECK, B. (1963) β-hydroxylation of tyramine in vivo. *Acta Pharmacologica et Toxicologica (København)*, **20**, 371–4.

CHIDSEY, C. A., HARRISON, D. C. and BRAUNWALD, E. (1962) Release of norepinephrine from the heart by vaso-active amines. *Proceedings of the Society for Experimental Biology and Medicine*, **109**, 488–490.

CHOKROVERTY, S., BARRON, K. D., KATZ, F. H., DEL GRECO, F. and SHARP, J. T. (1969) The syndrome of primary orthostatic hypotension. *Brain*, **92**, 743–768.

CREVELING, C. R., LEVITT, M. and UNDENFRIEND, S. (1962) An alternative route for the biosynthesis of norepinephrine. *Life Sciences*, **1**, 523–526.

DAVIES, B., BANNISTER, R. and SEVER, P. (1978) Pressor amines and monoamine-oxidase inhibitors for treatment of postural hypotension in autonomic failure. *Lancet*, **i**, 172–175.

DEMANET, J. C. (1976) Usefulness of noradrenaline and tyramine infusion tests in the diagnosis of orthostatic hypotension. *Cardiology*, **61**, Supplement 1, 213–223.

ENGLEMAN, K., HORWITZ, D., MUELLER, P. S. and SJOERDSMA, A. (1964) Denervation hypersensitivity of adipose tissue in idiopathic orthostatic hypotension. *Lancet*, **ii**, 927–929.

GRAHAM, J. G. and OPPENHEIMER, D. R. (1969) Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 28–34.

HOHL, R. D., FRAME, B. and SCHATZ, I. J. (1965) The Shy-Drager variant of idiopathic orthostatic hypotension. *American Journal of Medicine*, **39**, 134–141.

HOLTON, P. and WOOD, J. B. (1965) The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects. *Journal of Physiology, London*, **181**, 365–378.

HOPKINS, A., NEVILLE, B. and BANNISTER, R. (1974) Autonomic neuropathy of acute onset. *Lancet*, **i**, 769–771.

IBRAHIM, M. M. (1975) Localisation of lesions in patients with idiopathic orthostatic hypotension. *British Heart Journal*, **37**, 868–872.

JOHNSON, R. H., LEE, G. DE J., OPPENHEIMER, D. R. and SPALDING, J. M. K. (1966) Autonomic failure with orthostatic hypotension due to intermediolateral column degeneration. *Quarterly Journal of Medicine*, **35**, 276–292.

—— and SPALDING, J. M. K. (1974) *Disorders of the Autonomic Nervous System*. Oxford: Blackwell, p. 79.

KONTOS, H. A., RICHARDSON, D. W. and NORVELL, J. E. (1975) Norepinephrine depletion in idiopathic orthostatic hypotension. *Annals of Internal Medicine*, **82**, 336–341.

MATHIAS, C. J., FRANKEL, H. L., CHRISTENSEN, N. J. and SPALDING, J. M. K. (1976) Enhanced pressor response to noradrenaline in patients with cervical spinal cord transection. *Brain*, **99**, 757.

—— MATTHEWS, W. B. and SPALDING, J. M. K. (1977) Postural changes in plasma renin activity and responses to vasoactive drugs in a case of Shy-Drager syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 138–143.

NANDA, R. N., BOYLE, F. C., GILLESPIE, J. S., JOHNSON, R. H. and KEOGH, H. J. (1977) Idiopathic orthostatic hypotension from failure of noradrenaline release in a patient with vasomotor innervation. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 11–19.

OKADA, F., YAMASHITA; I. and SUWA, N. (1975) Two cases of acute pandysautonomia. *Archives of Neurology, Chicago*, **32**, 146–151.

PARKS, V. J., SANDISON, A. G., SKINNER, S. L. and WHELAN, R. F. (1961) Sympathomimetic drugs in orthostatic hypotension. *Lancet*, **i**, 1133–1136.

SCHWARTZ, G. A. (1975) Dysautonomic syndromes in adults. In: *Handbook of Neurology*. Edited by P. J. Vinken and G. W. Bruyn Amsterdam: North-Holland, Vol. **22**, 243–280.

SEVER, P. S. and GORDON, D. (1978) Circulating catecholamines. *Proceedings of the Royal Society of Medicine*, Supplement 11, **70**, 44–47.

SHY, G. M. and DRAGER, G. A. (1960) A neurological syndrome associated with orthostatic hypotension. *Archives of Neurology, Chicago*, **2**, 511–527.

SMITH, A. D. (1973) Mechanisms involved in the release of noradrenaline from sympathetic nerves. *British Medical Bulletin*, **29**, 123–129.

TRENDELENBURG, U. (1962) Restoration by sympathomimetic of the response of isolated atria of reserpine-treated guinea-pigs to tyramine and dimethyl-phenyl-piperazinium iodide. *Federation Proceedings*, **21**, 332.

—— (1963) Supersensitivity and subsensitivity to sympathomimetic amines. *Pharmacological Reviews*, **15**, 225–276.

—— (1972) Factors influencing the concentration of catecholamines at the receptors. *Handbuch der experimentellen Pharmakologie*, **33**, 726–761.

VANDERHAEGHEN, J.-J., PÉRIER, O. and STERNON, J. E. (1970) Pathological findings in idiopathic orthostatic hypotension. *Archives of Neurology, Chicago*, **22**, 207–214.

WILCOX, C. S. and AMINOFF, M. J. (1976) Blood pressure responses to noradrenaline and dopamine infusions in Parkinson's disease and the Shy-Drager syndrome. *British Journal of Clinical Pharmacology*, **3**, 207–214.

YOUNG, R. R., ASBURY, A. K., CORBETT, J. L. and ADAMS, R. D. (1975) Pure pandysautonomia with recovery—description and discussion of diagnostic criteria. *Brain*, **98**, 613–636.

ZIEGLER, M. C., LAKE, C. R. and KOPIN, I. J. (1977) The sympathetic nervous system defect in primary orthostatic hypotension. *New England Journal of Medicine*, **296**, 293–297.

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Brain (1979), **102**, 177–192

PRIMARY IDIOPATHIC CEREBROVASCULAR AMYLOIDOSIS IN A CHILD

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INTRODUCTION

'CEREBRAL AMYLOIDOSIS' has been loosely used to describe various forms of amyloid or amyloid-like deposits in the central nervous system (CNS) in various pathological conditions. Amyloid may deposit in the CNS in the form of amorphous or radiating plaques (senile and Kuru plaques); in the wall of meningeal and parenchymal blood vessels (congophilic angiopathy, Pantelakis, 1954); in the perivascular spaces (dyshoric angiopathy, Morel and Wildi, 1952); in the perivascular neural parenchyma (Drüsige Entartung, Scholz, 1938); on the surface of the cerebrum or ventricular wall; free in the parenchyma; in the subpial region, subarachnoid space, or choroid plexus; or in the form of localized nodular masses. Vascular degenerations referred to as hyaline thickening or colloidal degeneration in the old literature may or may not represent amyloid deposits in the blood vessel wall. The neurofibrillary material in neurons in Alzheimer's presenile and senile dementia was once considered to be amyloid because of its congophilia, metachromasia and birefringency (Divry, 1952), and the concept is still supported by some investigators (Schwartz, 1970) who use cerebral amyloidosis almost synonymously with Alzheimer's disease and senile dementia; but the amyloid nature of these neurofibrillary changes has been ruled out by recent electron microscopic studies (Terry, Gonatas and Weiss, 1964; Kidd, 1964; Luse and Smith, 1964; Krigman, Feldman and Bensch, 1965).

Pathological conditions which may accompany or lead to amyloid deposits in various constituents of the CNS are numerous and heterogeneous in ætiopathogenesis. If we wish to continue to use the term 'cerebral amyloidosis' to include all of these conditions, we must subdivide them into at least the following four groups:

1. primary idiopathic cerebral amyloidosis;
2. secondary (or reactive) cerebral amyloidosis;
3. disseminated cerebral amyloidosis;
4. other or miscellaneous types.

Primary idiopathic cerebral amyloidosis is almost always discussed in conjunction with Alzheimer's disease and related ageing processes. In this group amyloid is deposited in senile plaques and in amyloid angiopathy. The former is the common, almost constant feature which almost always accompanies Alzheimer's neurofibrillary changes in presenile and senile dementia, but which may be found independently in the brains of old people without clinical dementia. The latter is less common and inconstant, almost always accompanying senile plaques only as an ancillary feature. Ulrich, Taghavy and Schmidt (1973) called congophilic angiopathy the vascular form and senile plaques the parenchymatous form of cerebral amyloidosis.

Reactive (or secondary) cerebral amyloidosis is usually manifested only by amyloid angiopathy, rarely accompanied by senile plaque formation, and is usually found focally around or in the lesions of old hæmorrhage (Torack, 1975), tumour (Morgenstern, 1934), radiation necrosis (Fischer and Holfelden, 1930; Foltz, Holyoke and Heyl, 1953), demyelinating foci (Heffner, Porro, Olson and Earle, 1976) or old scar. It can occur at any age.

Disseminated cerebral amyloidosis is a part of systemic amyloidosis but is rare (Marinesco, 1931; Krücke, 1950; Haberland, 1964). In addition to deposits in senile plaques and amyloid angiopathy, similar to those of primary idiopathic cerebral amyloidosis, free amyloid deposits are found in the subarachnoid and subpial regions and may form a thick layer deposited on the surface of the cerebral cortex and ventricular wall.

The miscellaneous cases which do not fit into any of the above three categories include cases with incidental amyloid deposits in otherwise distinct clinical or pathological entities such as Kuru disease (Klatzo, Gajdusek and Zigas, 1959), Creutzfeldt-Jakob disease (Chou and Martin, 1971; Krücke, Beck and Vitzthum, 1973), certain forms of scrapie in mice (Dickinson, 1970), or other known slow virus infections which are not considered as candidates for cerebral amyloidosis ordinarily.

The last three of these four groups present few conceptual problems, if only because there are so few examples. Classifying the first as an example of 'cerebral amyloidosis' does, however, present a conceptual problem because no one knows whether senile plaques and vascular amyloidosis are merely statistical concomitants or are biologically and significantly associated with other ageing processes, including neurofibrillary tangles and granulovacuolar degeneration. Put another way, how many of these phenomena are due to slow virus infections, to genetic predisposition, to metabolic changes or to other factors unrelated to ageing *per se*?

It is certainly not my intention to imply that cerebral amyloidosis is a synonym for or a principal feature of the ageing changes of the brain. The use of cerebral amyloidosis here is a provisional expedient for encompassing all the different forms of amyloid deposits in the CNS. Other investigators (Worster-Drought, Greenfield and McMenemey, 1940; Worster-Drought, 1944; Corsellis and Brierley, 1954; Neumann, 1960; Hollander and Strich, 1970; Ulrich *et al.*, 1973) have separated out from the group of senile and presenile changes a number of cases which have had diffuse amyloid angiopathy as their principal histological finding. Although these patients have been relatively young, in their third and fourth decades at the time of onset, they were still not young enough to be completely dissociated from the group of patients with Alzheimer's disease (Löken and Cyvin, 1954; Malamud and Lowenberg, 1929). Indeed, some of these cases had other superimposed ageing changes in the CNS which made their complete separation from Alzheimer's disease difficult. Furthermore, some investigators (Van Bogaert, 1970) consider amyloid angiopathy, regardless of its severity, as merely non-specific, only one aspect of many expressions of ageing processes.

The case to be presented in this report was a boy who was 14 years old at the time of death. The onset of progressive physical disability and mental deterioration was gradual and could be traced back at least to the age of 10 years. The entire CNS, including not only the cerebral cortex but also the cerebral white matter, basal ganglia, brain-stem, cerebellar cortex and white matter and spinal cord, was involved by extensive amyloid angiopathy, senile plaques, perivascular amyloid exudates (Drüsige Entartung, Scholz, 1938) and intraparenchymatous amyloid nodules. The histological appearances of each amyloid plaque and of the involved blood vessels are very similar to those seen in patients with presenile and senile dementia; but the distribution and predominance of the amyloid angiopathy and plaques, and the absence of Alzheimer's neurofibrillary changes in neurons, are distinctly different from those of presenile and senile dementia. Since the histopathological findings resemble much more those cases reported by Worster-Drought *et al.* (1940, 1944), Corsellis and Brierley (1954), Lüers (1947), Van Bogaert, Maere and de Smedt (1940) and Neumann (1960), the present case supports the view that idiopathic cerebrovascular amyloidosis is a distinct entity, different from Alzheimer's presenile and senile dementia, and primarily manifested by amyloid angiopathy of the CNS.

CASE REPORT

The patient was a boy who was fourteen years old at the time of his death. His father was of Russian stock and his mother of German descent. There was no family history of any known mental or neurological disease. The patient had 2 older siblings who were normal. He was first examined at aged 11 years (November 1971) for intellectual deterioration and inco-ordination, the onset of which had been gradual and could be traced retrospectively to about aged 10 years. A rectal biopsy obtained in November 1971 was said to reveal storage material in the ganglion cells, his EEG was epileptiform, and he was diagnosed as having Batten-Spielmeyer-Vogt disease. In April 1972 physical examination showed an obese, dysarthric and sluggish boy who walked stooped over, bent at the knees and hips. He had limited upward gaze, questionable non-macular vision in the left, abnormal ocular fundi with pigmentary degeneration of the macula, hyperactive deep tendon reflexes with sustained ankle clonus, bilateral Babinski signs, moderate spasticity (worse in the legs than in the arms), ataxia and Romberg's sign. There was a small right subcapsular cataract. EEG was abnormally slow and mildly epileptiform. Urine screen for mucopolysaccharides was negative. The patient also had skin lesions suggesting epidermolysis bullosa in the extremities and trunk; these had been present for three years, but a skin biopsy in May 1972 showed only subacute dermatitis.

The family moved from Colorado to Washington in January 1974. He was admitted to Children's Orthopedic Hospital, Seattle, on January 30, 1974 because of a decubitus ulcer on the right hip. At that time it was said that the patient had not walked for six months. His extremities were weak and wasted. He responded to pain and the simplest commands, but was unable to speak, only uttering sounds. He had difficulty in swallowing and choked frequently. Seizures, which had been only occasional in May 1972, had increased to one per day and included jerking of the mouth and upper limbs. He had been treated with dilantin since 1972. Neurological examination in March 1974 showed frequent yawning and chewing movements, positive snout reflex and glabellar rugæ. He could not sit unsupported, could not speak intelligibly, and did not respond to hand clapping, but was able to see and follow an object with his eyes. The ocular fundi appeared normal. The gag reflex was absent and the soft palate was slightly elevated. Muscle tone was increased with contractures of both elbows and knees. Deep tendon reflexes were markedly hyperactive in all extremities. Babinski's sign was present bilaterally. He responded to deep pain in all extremities. The patient was seen in the clinic again in September 1974 when his condition was essentially unchanged. His seizures were under good control with dilantin 200 mg a day.

The patient died in October 1974 following a cold for several days. The autopsy was performed by Dr. L. Samuel Vickers of Port Angeles, Washington. Other than bronchopneumonia, no pertinent pathological findings were found in the viscera. Extensive searches for amyloid deposits in the lungs, heart, kidneys, spleen, adrenals, intestines and other tissues revealed only mild congophilia in occasional arterial walls in the spleen and renal medulla and none in the heart, skeletal muscles and peripheral nerves.

RESULTS

Neuropathological Findings

The fresh whole brain weighed 1030 g. The leptomeningeal blood vessels were diffusely and markedly congested. The brain showed no lesion externally. Coronal sections of the cerebrum revealed the ventricular system to be moderately and symmetrically dilated. The corpus callosum appeared slightly thin and the centrum semiovale was thought to be slightly reduced in volume.

Sagittal and parasagittal sections of the cerebellum revealed focal areas of gritty granularity and dark brown discolouration in the deep folia of the right cerebellar hemisphere.

Horizontal sections of the brain-stem showed marked atrophy and gray discolouration of the pyramids in the medulla. The spinal cord was grossly normal.

Histological Findings

Blocks were taken from various areas of the cerebral hemispheres, basal ganglia, brain-stem, cerebellum and spinal cord, embedded in paraffin, sectioned 5 to 15 μm thick and stained with hæmatoxylin and eosin (H and E), luxol fast blue periodic-acid-Schiff hæmatoxylin (LFB-PAS-H), luxol fast blue (LFB), periodic-acid-Schiff (PAS), Gomori's trichrome, congo red, van Giesen, Holmes' axon stain and Holzer's glia stain.

Histological changes in the whole CNS were similar, involving all structures with some variations in severity in different anatomical areas. In general, the changes were much more severe in the grey matter than in the white matter, and more pronounced in the cerebellar folia than in the cerebral cortex. The least involved was the white matter of the spinal cord.

The most conspicuous findings were a marked prominence of thick-walled capillaries, and a mixture of PAS-positive and congophilic perivascular and free plaques. Capillaries, sectioned in various directions, were exuberant, especially in the cerebral and cerebellar cortices. With LFB-PAS-H stain (fig. 1) the walls of the capillaries were thickened, strongly PAS-positive, and stained strongly with Holmes' axon, Gomori's trichrome, congo-red and van Giesen stains. From the wall, slightly paler filaments radiated outward into the neural parenchyma. In cross sections, these filaments radiated, but in oblique or longitudinal sections of capillaries they were arranged in parallel and brush-like rows. Curved or linear longitudinal sections of capillaries with these brushy filaments were reminiscent of hairy caterpillars. In the periphery of these radiating or brush-like filaments there was a crown or row of numerous argyrophilic fibrils and granules, similar

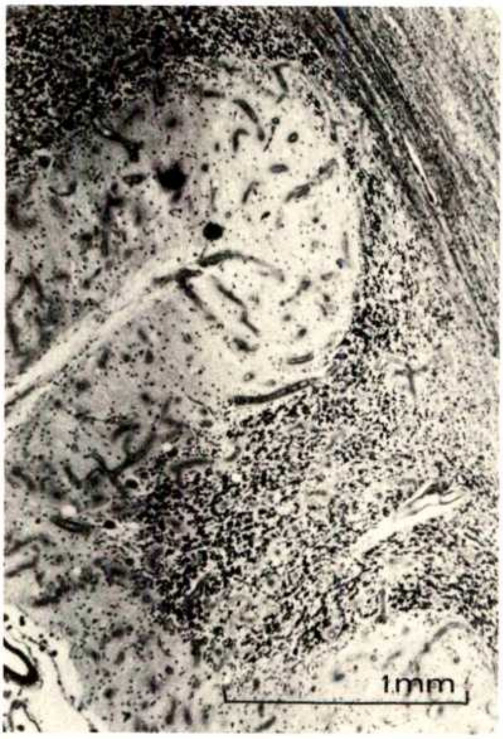

FIG. 1. Exuberant capillaries with thickened wall and amyloid plaques in all layers of the cerebellar cortex. LFB-PAS-H stain.

to those seen in senile plaques in Holmes' stain (fig. 2). These perivascular brush-like filaments were also congophilic, but less intense than the capillary wall. The congophilic material which formed the core of plaques, the radiating pericapillary filaments and the thickened capillary walls, was interpreted as amyloid because it was birefringent and showed orange-green dichroism under polaroid filters (fig. 3). This interpretation was further sustained by the electron-microscopic findings (see below).

Among these prominent capillaries and perivascular plaques there were numerous plaques which, though morphologically not very different from those of senile plaques, tended to have peripheral radial fibrils as seen in Kuru plaques (Klatzo *et al.*, 1959) (figs. 3, 4, and 5). These plaques were essentially similar to the perivascular plaques seen in cross-section except that a centrally located capillary was absent. They differed from Kuru plaques, which are found in Kuru and Creutzfeldt-Jakob disease (Chou and Martin, 1971; Krucke *et al.*, 1973), in that argyrophilic degenerated neurites were present, as in senile plaques, and their distribution was not limited to the cerebellar cortex. Plaques consisting of argyrophilic granules but devoid of a central congophilic core were also present. On the other hand, amyloid nodules without peripheral neurites were also found.

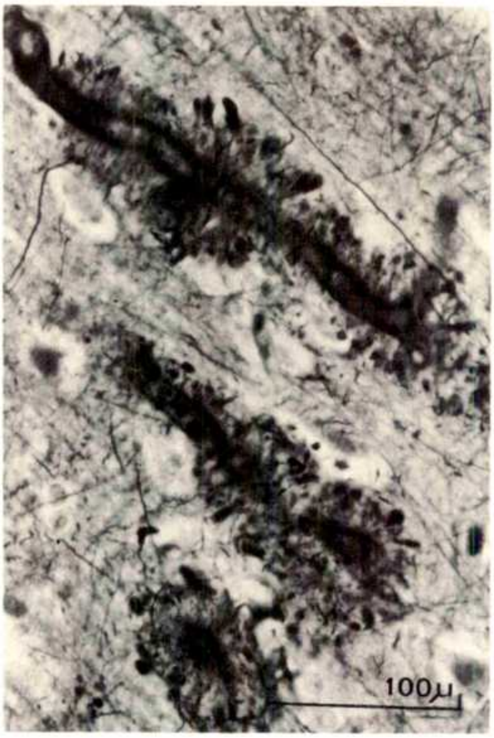

FIG. 2. Longitudinal, oblique and cross sections of capillaries showing amyloid angiopathy. Parallel brush-like fibrils radiate outward from the capillary walls. Numerous argyrophilic granules tend to be in the periphery of the fibrillary brushes. Holmes stain.

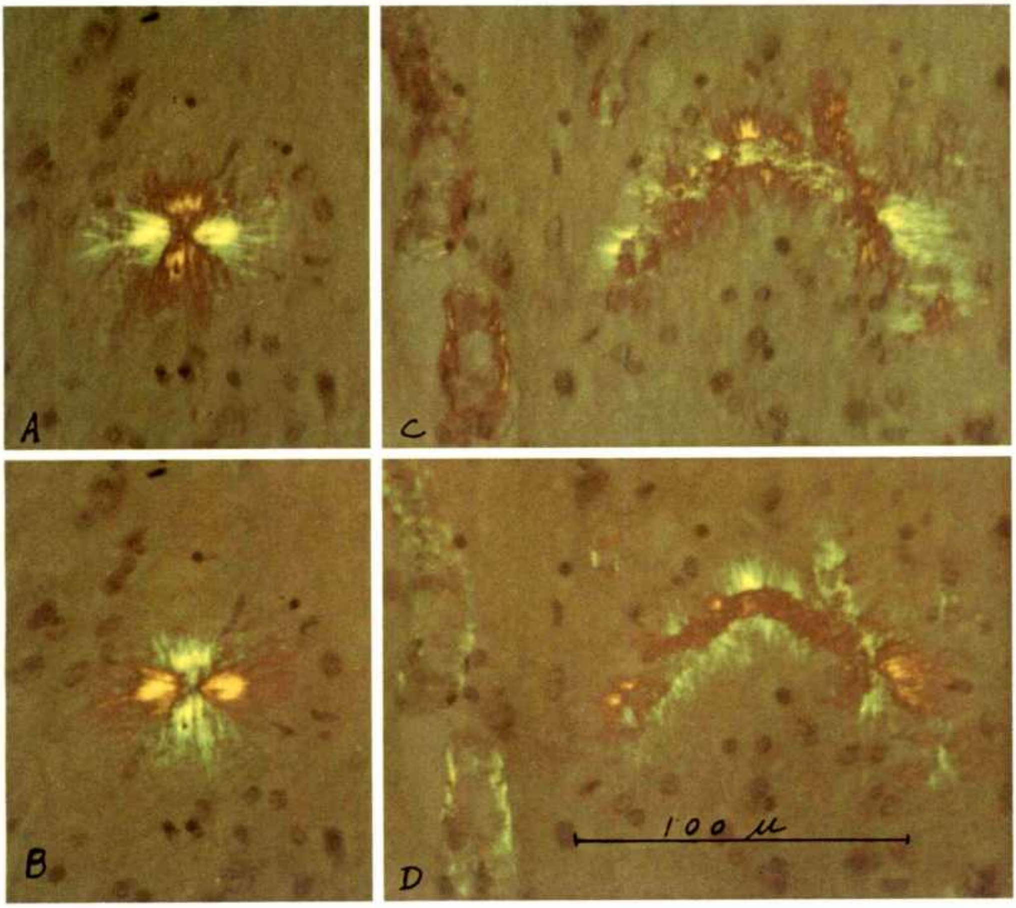

FIG. 3. Two sets of photomicrographs showing orange-green dichroic birefringence of an amyloid plaque (A and B) and a pericapillary amyloid brush (C and D). The two slightly larger blood vessels in C and D show amyloid only in their walls but not in the perivascular regions. Congo-red stain.

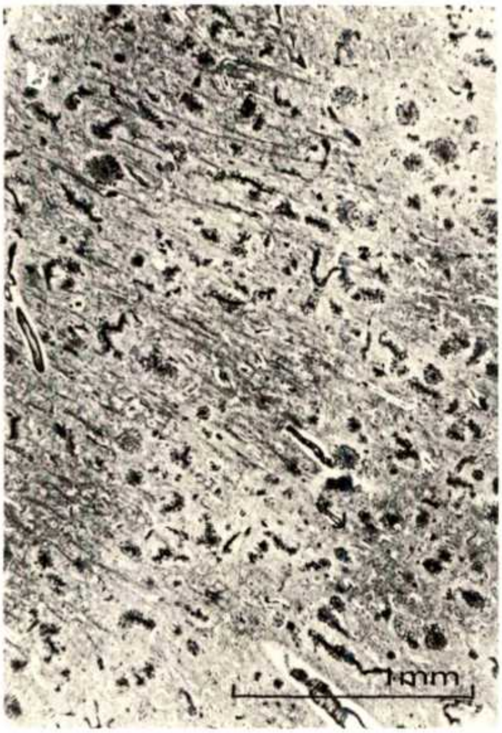

FIG. 4. Numerous amyloid plaques and amyloid angiopathy in the deeper layers of the cerebral cortex. Holmes stain.

Selected blocks were serially sectioned to determine the relationships of the 'free' plaques. Most of them were found to be merely tangential sections of perivascular plaques, but we were not able to prove to our satisfaction that all amyloid plaques were related to capillaries.

In spite of pronounced capillary and pericapillary amyloidosis with abundant plaques, neural elements in the cortex and myelinated fibres in the white matter were remarkably spared. In places, neuronal lamination was disorganized, but this appeared to be the result of distortion and displacement of neurons by prominent and expanding pericapillary amyloid deposits. Neurofibrillary degeneration of neurons was very rare. Degenerated neurites in the periphery of plaques were sometimes thick and formed small cones suggesting a portion of a neuron with neurofibrillary degeneration, but neurofibrillary changes of whole neurons, characteristic of Alzheimer's disease, were not found. Granulovacuolar degeneration of Simchowicz was not found in the hippocampus.

Congophilic birefringent and dichroic amyloid deposits were present in the walls of larger arteries and arterioles in the brain parenchyma (fig. 3), as well as in the leptomeninges and choroid plexus. Amyloid deposits in these larger vessels usually involved only the vascular wall and were frequently focal. No perivascular brushy filaments or argyrophilic granules were found in the larger vessels. Calcification occurred focally in capillaries with marked pericapillary amyloidosis in the cerebellum. The lumen of these calcified capillaries was often obliterated.

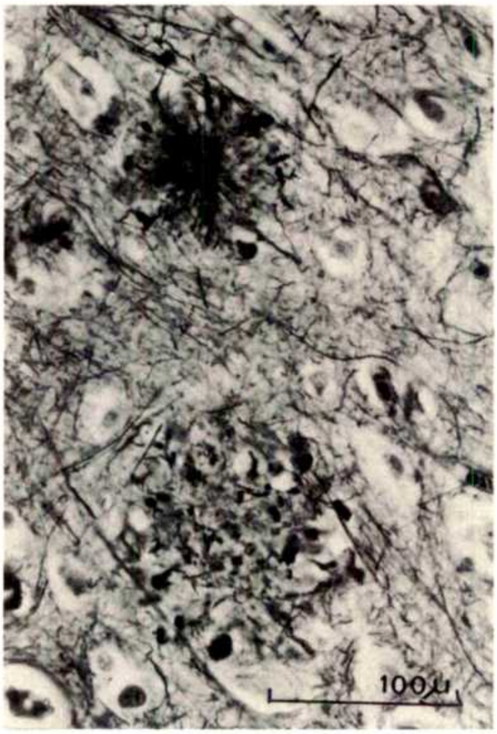

FIG. 5. An amyloid plaque with a radiating fibrillary core (*top*) and another showing amorphous mixture of argyrophilic granules and ground substance. Holmes stain.

Electron Microscopic Findings

Post-mortem specimens from the cerebrum and cerebellum were post-fixed in 4 per cent glutaraldehyde and studied under an electron microscope following further fixation in osmium tetroxide, embedding in epon and sectioning. The endothelial cells of affected capillaries were poorly preserved, the capillaries being represented by a thick ring of packed filaments of about 10 nm. These filaments formed interwoven, small bundles which were usually short, irregularly curved and arranged in a somewhat disorderly way, but tended to be concentric in the internal portion of the ring and radiating outward into the neural tissue. They were relatively thick at first, then gradually tapered out and finally faded into the tissue (figs. 6, 7, and 8). The whole picture reminded one of a volcano with lava running in all

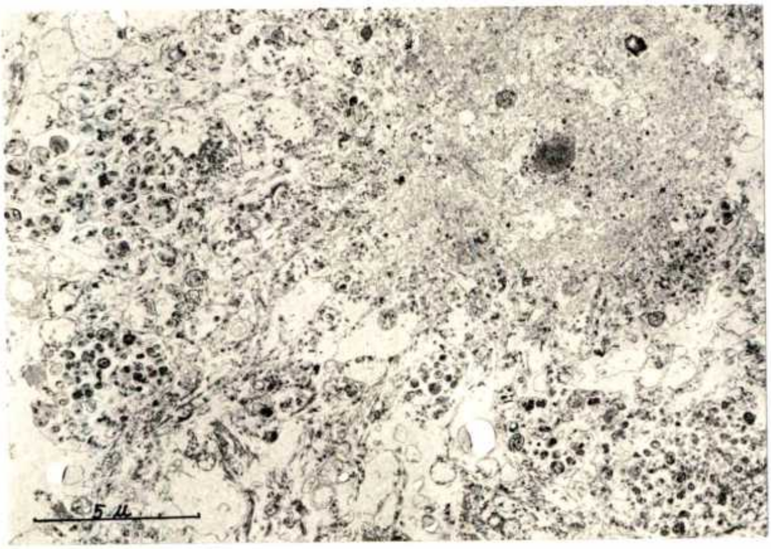

FIG. 6. Electron micrograph of an amyloid plaque showing a fibrillary core with processes radiating outwards. Clusters of degenerated mitochondria intermix with processes and surround the fibrillary core.

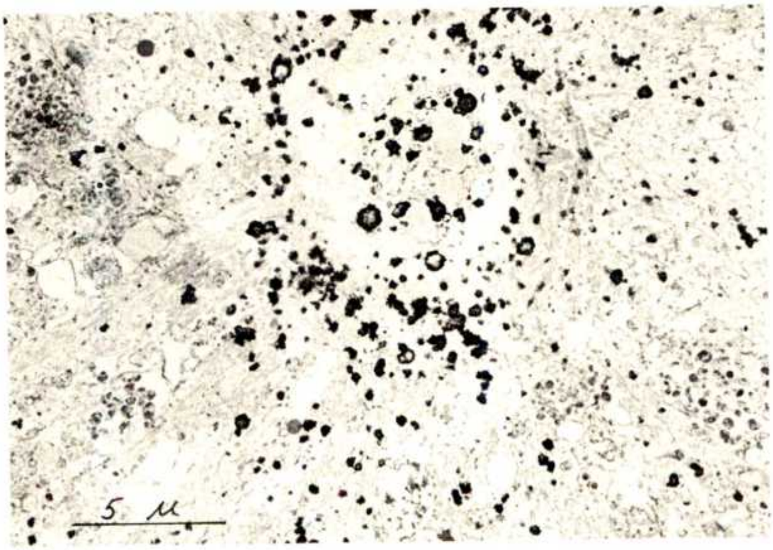

FIG. 7. Electron micrograph of a perivascular plaque showing numerous calcium granules in the degenerated capillary wall and radiating processes.

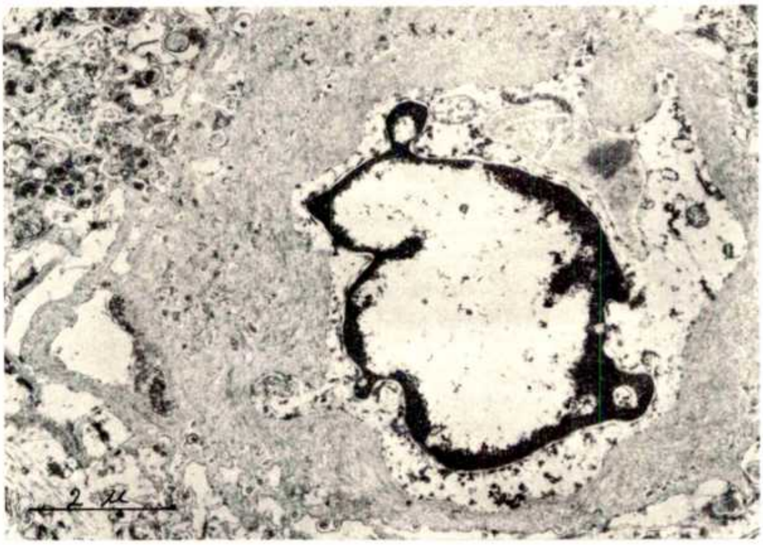

FIG. 8. Higher magnification of a capillary showing an endothelial cell in the centre surrounded by a thick fibrillary wall.

directions. No basement membrane was present around the affected capillaries; instead, this site was occupied by bundles of amyloid fibrils. Among radiating branches of filaments were neuritic processes, synaptic vesicles and glial processes, some of which were relatively well preserved and easily recognizable. Others, however, were unidentifiable vesicles and granules of various sizes and shapes. Conspicuous structures were clusters of moderately dense granules in the periphery and between radiating branches of filaments. These clusters were often membrane-bound. Calcification granules were seen both in the ring and in the branches of the amyloid fibrils but more commonly were centrally located. Occasional axons with regularly arranged microtubules were also present. These microtubules were 20 to 25 nm in diameter and were twisted with regular intervals. Masses of radiating fibrils without central capillaries were more common than perivascular radiating fibrils.

DISCUSSION

The histochemical, light and electron microscopic characteristics of the material found in the blood vessel walls in the leptomeninges and cerebral parenchyma, in the perivascular regions of the neural parenchyma and in the central core of free plaques of this 14-year-old boy are those of amyloid. Small amounts of similar material were found in the walls of occasional arteries of the spleen and kidney but are certainly minor, almost negligible, in comparison to the degree of CNS involvement, hardly sufficient for consideration of a diagnosis of systemic amyloidosis in this case.

The macro- and microscopic studies of the CNS showed no other underlying disease of the CNS which could induce reactive cerebral amyloidosis. By all criteria, this case falls into the category of primary idiopathic cerebrovascular amyloidosis.

The patient cannot be considered as a case of atypical or juvenile Alzheimer's disease in spite of the fact that common neurohistological findings represented by the combined 'senile plaques' and amyloid angiopathy of all types were present in both. There are more dissimilarities than similarities present between our patient and patients with Alzheimer's disease:

(1) he was only 14 years old at the time of death and the onset of the disease was at the age of 10 years. The discrepancy of age of onset is too great, even if one accepts the concept of premature ageing as frequently seen in patients with Down's syndrome (Burger and Vogel, 1973; Jervis, 1948; Neumann, 1967; Olsen and Shaw, 1969);

(2) senile plaques and amyloid angiopathy tend to occur together in Alzheimer's disease, although senile plaques are more constant than amyloid angiopathy. The incidence of amyloid angiopathy in Alzheimer's disease ranges from 12 to 87 per cent, apparently increasing with age (Scholz, 1938; Surbek, 1961; Mandybur, 1975). Senile plaques can be found in the brains of aged individuals without amyloid angiopathy, but amyloid angiopathy almost always occurs with senile plaques. These observations suggest that amyloid angiopathy is of secondary importance relative to senile plaques in Alzheimer's disease, whereas amyloid angiopathy and perivascular plaques were the predominant picture in our case;

(3) neuronal degeneration in the form of Alzheimer's neurofibrillary degeneration and neuronal loss is another essential feature of Alzheimer's disease, whereas neurofibrillary degeneration was not found and the neurons were relatively spared in our case;

(4) senile plaques in Alzheimer's disease are always formed in the matrix of the gray matter, usually of the cerebral cortex, and their vascular relationship is infrequent and inconstant (Margolis, 1959). They practically never occur in the white matter, cerebellum and spinal cord, whereas the CNS of this case, including the white matter, was indiscriminately involved by similar plaques, and the most severely involved region was the cerebellar cortex;

(5) the histological appearances of the plaques in our case are not exactly identical to the usual senile plaques. The present plaques were strongly PAS-positive and stained quite well with practically any stain. The peripheral radiation of the amyloid core resembles 'Kuru plaques' more than senile plaques. In addition, the abundance of perivascular plaques conforms with the prevailing amyloid angiopathy and is unusual for Alzheimer's disease.

Thus, I am convinced that the amyloid plaques seen in this patient are different from the senile plaques seen in senile and presenile dementia because of their histological appearances, anatomical distribution and vascular relationship. However, I am not certain about the pathogenetic relationship between the plaques seen in this case and the plaques found in other conditions, such as Kuru, Creutzfeldt-Jacob disease, experimental scrapie (Bruce and Fraser, 1975) and aged dogs (Wisniewski, Johnson, Raine, Kay and Terry, 1970). Morphologically the plaques in our patient resemble Kuru plaques and the stellate plaques of experimental scrapie in mice, but not the plaques of aged dogs. The distribution and vascular relation simulate those of experimental scrapie in mice but not those of Kuru and Creutzfeldt-Jacob disease. The major differences between this case and experimental scrapie in mice are in the intensity of plaques and the predominance of the amyloid angiopathy.

I cannot concur with the concept of Morel and Wildi (1952) that 'senile' plaques are the result of dyshoria affecting capillaries of the gray matter, and that Drusige Entartung represents the dyshoric changes in precapillaries and arterioles, because abundant Drusige Entartung were observed in capillaries in our case. The concept of Morel and Wildi that amyloid angiopathy and amyloid plaques share the same ætiopathological mechanism, such as dyshoria of amyloid, is acceptable in explaining the histopathology of our case and may explain a handful of other reported cases in the literature, but probably does not adequately explain the similar histopathological findings in senile and presenile dementia.

In 16 cases found in the literature, the common feature was the exuberant amyloid angiopathy in the brain. All these cases showed some of the features of Alzheimer's disease in variable degree, as well as some features which were atypical for Alzheimer's disease, such as heredofamilial factors (Worster-Drought *et al.*, 1940, 1944; Van Bogaert *et al.*, 1940; Lüers, 1947; Corsellis and Brierley, 1954), relatively young age of patients (Van Bogaert *et al.*, 1940; Lüers, 1947; Neumann, 1960), and rapid onset or onset precipitated by trauma or other illnesses (Hollander and Strich, 1970; Peters, 1950).

The group may include cases of otherwise typical Alzheimer's disease with unusually prominent amyloid angiopathy (Benedek and McGovern, 1949) or atypical Alzheimer's disease, the early onset of which may be ascribed to some particular events (Hollander and Strich, 1970, Case 1). Most authors regarded their cases as a type of Alzheimer's disease in spite of notable atypical features, but Worster-Drought *et al.* (1940, 1944), Neumann (1960) and Ulrich *et al.* (1973) considered their cases to be different from Alzheimer's disease, despite some common features which they shared with Alzheimer's disease. McMenemey, one of the co-investigators of Worster-Drought's cases in 1940 and 1944, described them retrospectively (1970) as cases of familial cerebrovascular amyloidosis with Binswanger's disease. Corsellis and Brierley (1954) thought their cases formed a link between Alzheimer's disease, the amyloid form of senile vascular disease and the group of hereditary Alzheimer's disease.

The relatively inconspicuous Alzheimer's neurofibrillary changes in neurons, the abundant perivascular and free amyloid plaques with a tendency to involve the cerebellum and to extend into the cerebral and cerebellar white matter in the 2 cases of Worster-Drought *et al.* (1940, 1944), in the case of Neumann (1960), in Case 6 of Hollander and Strich (1970) and in the present case, together possibly with the case of Van Bogaert *et al.* (1940), the 2 cases of Lüers (1947), and the cases of Ulrich *et al.* (1973), are distinctly alien to those of Alzheimer's disease and related ageing processes. The present case, whose age was completely outside the range of Alzheimer's disease and was without histological overlap with Alzheimer's disease, serves as a key case to support the original idea of Worster-Drought, Greenfield and McMenemey that primary cerebrovascular amyloidosis is a distinct entity.

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REFERENCES

BENEDEK, S. and MCGOVERN, V. J. (1949) A case of Alzheimer's disease with amyloidosis of the vessels of the cerebral cortex. *Medical Journal of Australia*, **36** (2), 429–430.

BRUCE, M. E. and FRASER, H. (1975) Amyloid plaques in the brains of mice infected with scrapie: Morphological variation and staining properties. *Neuropathology and Applied Neurobiology*, **1**, 189–202.

BURGER, P. C. and VOGEL, F. S. (1973) The development of the pathologic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. *American Journal of Pathology*, **73**, 457–476.

CHOU, S. M. and MARTIN, J. D. (1971) Kuru-plaques in a case of Creutzfeldt-Jakob disease. *Acta Neuropathologica, Berlin*, **17**, 150–155.

CORSELLIS, J. A. N. and BRIERLEY, J. B. (1954) An unusual type of presenile dementia (atypical Alzheimer's disease with amyloid vascular change). *Brain*, **77**, 571–587.

DICKINSON, A. G. (1970) Classification of scrapie agents based on histological and incubation period criteria in mice. In: *Proceedings of the VIth International Congress of Neuropathology, Paris.* Amsterdam: Excerpta Medica, pp. 841–842.

DIVRY, P. (1927) Étude histochemique des plaques séniles. *Journal de Neurologie et der Psychiatrie, Bruxelles*, **27**, 643–657.

—— (1952) La pathochimie générale et cellulaire des processus séniles et préséniles. In: *Proceedings of the 1st International Congress of Neuropathology, Rome.* Amsterdam: Excerpta Medica, Vol. 2, pp. 313–345.

FISCHER, A. W. and HOLFELDEN, H. (1930) Lokales Amyloid im Gehirn. Eine Spätfolge von Röntgenbestrahlungen. *Deutsche Zeitschrift für Chirurgie*, **227**, 475-483.

FOLTZ, E. L., HOLYOKE, J. B., HEYL, H. L. (1953) Brain necrosis following x-ray therapy. *Journal of Neurosurgery*, **10**, 423-429.

GUDMUNDSSON, G., HALLGRÍMSSON, J., JÓNASSON, T. A. and BJARNASON, Ó. (1972) Hereditary cerebral hæmorrhage with amyloidosis. *Brain*, **95**, 387-404.

HABERLAND, C. (1964) Primary systemic amyloidosis: cerebral involvement and senile plaque formation. *Journal of Neuropathology and Experimental Neurology*, **23**, 135-150.

HEFFNER, R. R., PORRO, R. S., OLSON, M. E. and EARLE, K. M. (1976) A demyelinating disorder associated with cerebrovascular amyloid angiopathy. *Archives of Neurology, Chicago*, **33**, 501-506.

HOLLANDER, D. and STRICH, S. J. (1970) Atypical Alzheimer's disease with congophilic angiopathy presenting with dementia of acute onset. In: CIBA Foundation Symposium on *Alzheimer's Disease and Related Conditions*. London: Churchill, pp. 105-124.

JERVIS, G. A. (1948) Early senile dementia in mongoloid idiocy. *American Journal of Psychiatry*, **105**, 102-106.

KIDD, M. (1964) Alzheimer's disease—an electron microscopical study. *Brain*, **87**, 307-321.

KLATZO, I.; GAJDUSEK, D. C. and ZIGAS, V. (1959) Pathology of kuru. *Laboratory Investigation*, **8**, 799-847.

KRIGMAN, M. R., FELDMAN, R. G. and BENSCH, K. (1965) Alzheimer's presenile dementia. A histochemical and electron microscopic study. *Laboratory Investigation*, **14**, 381-396.

KRÜCKE, W. (1950) Das Zentralnervensystem bei generalisierter Paramyloidose. *Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **185**, 165-192.

—— BECK, E. and VITZTHUM, H. G. (1973) Creutzfeldt-Jakob disease. Some unusual morphological features reminiscent of Kuru. *Zeitschrift fur Neurologie*, **206**, 1-24.

LÖKEN, A. C. and CYVIN, K. (1954) A case of clinical juvenile amaurotic idiocy with the histological picture of Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 211-215.

LÜERS, Th. (1947) Über die familiäre juvenile Form der Alzheimerschen Krankheit mit neurologischen Herderscheinunger. *Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **179**, 132-145.

LUSE, S. A. and SMITH, K. R., Jr. (1964) The ultrastructure of senile plaques. *American Journal of Pathology*, **44**, 558-563.

MALAMUD, W. and LOWENBERG, K. (1929) Alzheimer's disease, a contribution to its etiology and classification. *Archives of Neurology and Psychiatry, Chicago*, **21**, 805-827.

MANDYBUR, T. I. (1975) The incidence of cerebral amyloid angiopathy in Alzheimer's disease. *Neurology, Minneapolis*, **25**, 120-126.

MARGOLIS, G. (1959) Senile cerebral disease: A critical survey of traditional concepts based upon observations with newer techniques. *Laboratory Investigation*, **8**, 335-370.

MARINESCO, G. (1931) Sur une affection particulière simulant, au point de vue clinique, la sclérose en plaques et ayant pour substratum des plaques spéciales du type sénile. *Archives Roumaines de Pathologie Expérimentale et de Microbiologie*, **4**, 41-49.

MCMENEMEY, W. H. (1970) Discussion. In: CIBA Foundation Symposium on *Alzheimer's Disease and Related Conditions.* London: Churchill, pp. 132-133.

MOREL, F. and WILDI, E. (1952) General and cellular pathochemistry of senile and presenile alteration of the brain. *Proceedings of the 1st International Congress of Neuropathology, Rome.* Amsterdam: Excerpta Medica, Vol. 2, pp. 347-374.

MORGENSTERN, Z. I. (1934) Ein Fall von lokalem Amyloid der Hirngefässe. *Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, **294**, 334-339.

NEUMANN, M. A. (1960) Combined amyloid vascular changes and argyrophilic plaques in the central nervous system. *Journal of Neuropathology and Experimental Neurology*, **19**, 370-382.

—— (1967) Langdon Down syndrome and Alzheimer's disease. *Journal of Neuropathology and Experimental Neurology*, **26**, 149-150.

OLSON, M. I. and SHAW, C.-M. (1969) Presenile dementia and Alzheimer's disease in Mongolism. *Brain*, **92**, 147-156.

PANTELAKIS, S. (1954) Un type particular d'angiopathie sénile du système nerveux central: l'angiopathie congophile, topographe et fréquences. *Monatsschrift für Psychiatrie und Neurologie*, **128**, 219-254.

PETERS, G. (1950) Über paramyloidose des Gehirns. *Verhandlungen der Deutschen Gesellschaft für Pathogie*, **32**, 83-89.

SCHOLZ, W. (1938) Studien zur Pathologie der Hirngefässe, II. Die drüsige Entartung der Hirnarterien und—capillaren. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **162**, 694-715.

SCHWARTZ, P. (1970) *Amyloidosis, Cause and Manifestation of Senile Deterioration.* Springfield: Charles C. Thomas, pp. 42-79.

SURBEK, B. (1961) L'angiopathie dyshorique (Morel) de l'écorce cérébrale. Étude anatomo-clinique et statistique, aspect génétique. *Acta Neuropathologica*, **1**, 168-197.

TERRY, R. D., GONATAS, N. K. and WEISS, M. (1964) Ultrastructural studies in Alzheimer's presenile dementia. *American Journal of Pathology*, **44**, 269-298.

TORACK, R. M. (1975) Congophilic angiopathy complicated by surgery and massive hemorrhage. *American Journal of Pathology*, **81**, 349-366.

ULRICH, G., TAGHAVY, A. and SCHMIDT, H. (1973) Zur Nosologie und Ätiologie der kongophilen Angiopathie (Gefässform der cerebralen Amyloidosen). *Zeitschrift fur Neurologie*, **206**, 39-59.

VAN BOGAERT, L. (1970) Cerebral amyloid angiopathy and Alzheimer's disease. In: CIBA Foundation Symposium on *Alzheimer's Disease and Related Conditions.* London: Churchill, pp. 95-104.

—— MAERE, M. and DE SMEDT, E. (1940) Sur les formes familiales précoces de la maladie d'Alzheimer. *Monatsschrift für Psychiatrie und Neurologie*, **102**, 249-301.

WISNIEWSKI, H., JOHNSON, A. B., RAINE, C. S., KAY, W. J. and TERRY, R. D. (1970) Senile plaques and cerebral amyloidosis in aged dogs: A histochemical and ultrastructural study. *Laboratory Investigation*, **23**, 287-296.

WORSTER-DROUGHT, C. (1944) A form of familial presenile dementia with spastic paralysis. *Brain*, **67**, 38–43.

—— GREENFIELD, J. C. and MCMENEMEY, W. H. (1940) A form of familial presenile dementia with spastic paralysis (including the pathological examination of a case). *Brain*, **63**, 237–254.

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SUBJECTIVE REFERRAL OF THE TIMING FOR A CONSCIOUS SENSORY EXPERIENCE

A FUNCTIONAL ROLE FOR THE SOMATOSENSORY SPECIFIC PROJECTION SYSTEM IN MAN

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INTRODUCTION

PREVIOUS studies had indicated that there is a substantial delay, up to about 0·5 s, before activity at cerebral levels achieves 'neuronal adequacy' for eliciting a conscious somatosensory experience (Libet, Alberts, Wright, Delattre, Levin and Feinstein, 1964; Libet, 1966). The delay appeared necessary not only with stimulation of medial lemniscus, ventrobasal thalamus, or postcentral cortex, but even when the stimulus was a single electrical pulse at the skin (Libet, Alberts, Wright, and Feinstein, 1967, 1972; Libet, 1973). The present investigation began with an experimental test of whether there is in fact also a subjective delay in the conscious experience for a peripheral sensory stimulus. That is, is there a delay in the subjective timing of the experience that would correspond to the presumed delay in achieving the neuronal state that 'produces' the experience? The results of that test led to a modified hypothesis; this postulates (a) the existence of a subjective referral of the timing for a sensory experience, and (b) a role for the specific (lemniscal) projection system in mediating such a subjective referral of timing. Experimental tests of the new proposal were carried out and are reported here.

The timing of a subjective experience must be distinguished from that of a behavioural response (such as in reaction time), which might be made before conscious awareness develops; or even from minimum time intervals that are perceptually discriminable, since the question of *when* the subject becomes introspectively *aware* of the stimuli or of the discrimination is not answered by such measurements. There seemed to be no method by which one could determine the absolute timing of a subjective experience. Instead, we adopted a procedure in which the subject reported the subjective timing order of two sensory experiences. The validity of this procedure depended on the availability of a 'reference' sensation, with known constraints on its subjective timing, to which the timing for the peripherally-induced sensation could be meaningfully related. The reference sensation employed was that elicited by a stimulus applied directly to postcentral, somatosensory (SI) cortex. This cortical stimulus could be set experimentally so as to require a minimum train duration of up to about 0·5 s before it could elicit any conscious sensory experience (Libet *et al.*, 1964; Libet, 1966). Consequently, it could be assumed that the cortically-induced subjective experience could not 'arise' before the end of the experimentally fixed minimum train duration. (Preliminary reports of some of these findings have been made before the Society for Neuroscience in Toronto, Canada, November 7-11, 1976—*see* summary in *Brain Information Service Conference Report* No. 45, 1977, UCLA, Los Angeles, Ca. 90024, pp. 103-121; and in a symposium on *Cerebral Correlates of Conscious Experience*, *see* Libet, 1978).

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METHODS AND PROCEDURES

Subjects

Subjects were drawn from among two groups of patients in whom a stereotactic neurosurgical procedure was to be carried out, one with dyskinesias (chiefly parkinsonism or hereditary familial tremor) and another with chronic intractable pain. Only those patients were selected for the present studies whose physical and mental condition permitted them to give their fully informed consent, as well as the necessary degree of attention and responsiveness to somatosensory stimuli. Upon any indication of fatigue or loss of interest, or of a preference not to continue, the study session was terminated. All the investigational procedures have been reviewed (in relation to any possible risk factors and to the conditions of informed consent) and approved by an independent Committee on Protection of Human Subjects in Mount Zion Hospital (in accordance with guidelines set out by the National Institutes of Health, US Public Health Service). We note here our deep gratitude to the patients whose co-operation and interested participation made this type of investigation possible.

Stimulation and Recording Electrodes

The procedures employed were similar to those employed previously (Libet *et al.*, 1964, 1967, 1972). The subdural electrode assembly (Delgado, 1955) contained five or seven separate wires enclosed in a flat, flexible plastic carrier. Each wire has one uninsulated region about 1 mm long, and the exposed contacts for the separate wires are spaced 3 to 10 mm apart. (These assemblies are similar to those which have been used routinely for subdural explorations of cortical epileptigenic areas in certain epileptic patients).

The carrier is inserted posteriorly via a frontal burr hole made for therapeutic purposes; the insertion is done slowly and gently so that, in the occasional case when any obstruction is encountered, it could be halted and withdrawn. Such insertions of these subdural electrode assemblies and the temporary periods of stimulation with them have, in our experience with hundreds of patients since 1957, never resulted in any detectable signs of damage. To determine whether a given contact was located on the pre- or postcentral gyrus the motor and sensory responses to subsequent stimulation were tested. The subcortical contacts, in the ventroposterolateral or ventroposteromedial nuclei of thalamus (n.VPL or n.VPM), and in the medial lemniscus (LM) at a point just a few mm below the thalamus, were part of electrode assemblies (0·5 mm diameter) that were inserted to reach therapeutic targets (Feinstein, Alberts and Levin, 1969). Each uninsulated contact had an exposure length of 0·5 mm at right angles to the long axis of the subcortical assembly. Obviously the precise structure in which a contact lay could not be identified histologically. However, physiological evidence for location in n.VPL (or VPM) or in LM was considered to be confirmatory when stimulus trains of pulses with relatively low peak currents (0·1–0·2 mA) could produce a purely sensory response (usually a 'tingling', referred to a contralateral portion of the body), and when relatively small increases in stimulus strength gave large increases in the portion of the body to which the sensory response was referred. Production of any motor response by a cerebral stimulus had to be avoided, as the peripheral sensation generated by a muscular contraction could confuse the subjective timings for the test responses; fortunately, stimulus intensities must be raised far above the liminal sensory level at SI cortex of non-epileptic patients to produce any motor effects (Libet *et al.*, 1964), while in LM even very strongly supraliminal stimuli produce no motor responses (Libet *et al.*, 1967).

In each test trial two separate stimuli were presented in a temporally coupled fashion. The pair could consist of two peripheral stimuli (P_1–P_2); or, a 'Cerebral' stimulus replaced P_2, producing the pair P_1-Cerebral. Peripheral electrical stimuli (0·2–0·5 ms pulses) to the skin or median nerve were applied via two disc electrodes (Grass EEG type) separated by 1–2 cm. For a peripheral stimulus purely to skin the two electrodes were commonly applied to the back of the hand along a mediolateral axis; this usually results in the production of a sensation that is local and superficial in the skin, in contrast to one produced when stimulating a nerve bundle (Libet *et al.*, 1967). (In some experiments a visual flash constituted the P_1-peripheral stimulus; for this, a brief (0·01 ms) flash was delivered from a Grass photic stimulator, set at its lowest intensity and placed a metre or more away. The subject sat in a lighted room and usually did not gaze directly at the lamp. Under these conditions any visual after-image was minimized).

The 'Cerebral' stimulus could be applied either at the cortical (C) electrode, located subdurally on postcentral or SI cortex, or via a subcortical contact in n.VPL/VPM or in LM. Cerebral stimuli consisted of brief trains of constant current pulses, each 0·2–0·5 ms and usually at 60 pps, applied via one contact (unifocally); a large metal armband (over saline-soaked gauze) served as the second electrode. Peak currents for liminal stimuli were usually in the range of 1–3 mA for SI cortex and 0·1–0·2 mA for LM. The total coulombs passed was kept to a value well below that regarded as the threshold for producing irreversible tissue damage (Pudenz, Bullara, and Talalla, 1975; Bartlett, Doty, Lee, Negrão and Overman, 1977). This becomes especially important when purely unidirectional pulses are employed, as for the cortical stimuli. Stimuli to LM were usually biphasic in nature; either the successive pulses alternated in polarity (*see* Results, Section III-C, 2) or each pulse was capacitatively coupled.

Instructions to Subject

The subject was asked to report, within a few seconds after the delivery of each pair of temporally-coupled P_1-C stimuli, whether he subjectively experienced the peripherally-induced sensation (for P_1) first; or whether the cerebrally-induced sensation (for C) was first; or whether both appeared to him to start 'together' (at the same time). The subject was asked to pay attention to the *onset* of the two sensations.

In most experimental series, the sensation induced by a cerebral stimulus (sensation referred to an area on the contralateral side, commonly in the hand or arm region) was subjectively timed with respect to a P_1 stimulus that was applied to a related area of the hand or limb on the side opposite to that for the referred cerebrally-induced sensation; this allowed the subject to report simply—'right first' or 'left first', or 'together'. With many subjects in the earlier part of the study, the P_1 was a brief, weak flash of light; in these cases the subject reported 'flash first' or 'hand first' (the latter being the cerebrally-induced sensation) or 'together'. For the control or 'comparison' series of trials, in which the temporally-coupled stimuli were both peripheral ones (P_1–P_2), the nature of the subject's task and reporting was a similar one; the P_2-peripheral stimulus that replaced the experimental cerebral stimulus was placed on the skin generally within the referral area of the cerebrally-induced sensation.

General Procedure in an Experiment

The following features were common to most of the experiments in Section III of the 'Results and Discussion'. (They also apply with some obvious modifications to Section I, in which studies were carried out acutely in the operating room). After the patient recovered from the acute effects of the surgical procedure for intracranial implantation of electrodes, usually in two to three days, the responses to electrical stimulation at each electrode site were checked for the actual placement with respect to the intended structures.

The initial experimental phase usually consisted of a brief 'training' period. This consisted of 15 to 25 trials with temporally-coupled pairs of two peripheral stimuli; these were similar to trials to be used for the 'control' series except that, after his report of subjective order for the P_1-P_2 stimuli in each training trial, the subject was told the 'correct' answer (that is, the order in which the two peripheral stimuli were actually delivered in that trial). In addition to providing some familiarity with the procedure, the training series often quickly improved the consistency of responses obtainable in the following control series portion of the experiment when no information was given to the subject. Trials in the 'experimental series', with the temporally-coupled peripheral vs. cerebral stimuli, were subsequently started without further training; subjects were never given any information about the actual order of stimulus deliveries for peripheral-cerebral couplings.

In most series of trials with temporally-coupled stimuli, three different time intervals were employed for delivery of one stimulus of the pair relative to the P_1-peripheral stimulus, usually -200, 0 and $+200$ ms. For a number of subjects additional intervals were used (as in Tables 1-3). The particular coupling interval used in each given trial of a series was set by the operator just before each trial on the basis of a randomized sequence of numbers. Inter-trial intervals were kept to about 20 s with tests involving n.VPL or LM, 30 s with C (SI cortex), and 10–15 s when both coupled stimuli were purely peripheral.

For each individual trial, the subject was pre-alerted by the word 'ready', given orally by the observer who was in the room with the subject. Within a second or two, the actual trial period was initiated by an operator who was located in a control booth just outside the closed room in which the subject and the observer sat. The trial was initiated by a brief alerting tone signal and was followed by the two test stimuli which were separated by the preset coupling time interval. A fixed time period of 600 ms between the alerting tone and the P_1 test stimulus helped the subject to focus his attention during the required time. Neither the observer nor the subject were given any indication (either before or after a trial) of the specific coupling time interval used in any of the tests. However, the subject was told in advance that the time intervals, between each pair of test stimuli, might be changed in a random manner for each succeeding trial in the series; and that he was therefore to try to ignore and not be influenced by any particular pattern of the reports that he might make. Guessing about the sequential order of the two sensations was discouraged; the subject was asked to report his actual conscious experience of the order. When a subject occasionally 'missed', that is, found himself unable to report the timing order without guessing, because of a lapse in attention or memory, the same trial was repeated. The latter procedure conforms to our objective of studying the relative subjective timings of reportable awarenesses, not the ability to detect a timing order without necessarily consciously experiencing the order.

Establishment of Stimulus Values for Tests in an Experiment

The procedure for determining the threshold intensity (I) and minimum train duration (TD) at a given cerebral site were similar to those previously employed (Libet *et al.*, 1964; Libet, 1973). (Liminal I is the lowest peak-current level for a train of stimulus pulses which can elicit any conscious sensory experience; for SI cortex, n.VPL or LM, a minimum train duration of 'utilization TD' [U-TD] of about 0·5 s is required with liminal I—*see* Libet *et al.*, 1964; Libet, 1973). For stimuli to SI cortex, liminal I and U-TD values remain consistent (to within about ±10 per cent or less) when individual stimulus tests are repeated, if the intervals between tests are about 30 s or more (Libet *et al.*, 1964). However, when the stimulus to one of the cerebral sites was temporally coupled with a peripheral stimulus, as required in the present study, and when such paired stimuli were presented repeatedly at regular intervals in an experimental series, the subject's conscious responses to the cerebral stimulus tended to drop out (reversibly). In order to retain positive responses in the series without intolerable interruptions, intensity was raised somewhat above liminal I, to a level which reduced the minimum TD requirement to 200 to 300 ms. (Increases in TD above the U-TD of about 500 ms, when using a liminal I train, did not appear to eliminate this difficulty).

In most experimental series, therefore, the pulse intensity 'I' for the cerebral stimulus was set at a value such that the minimum required train duration was reduced to (but not below) a value of 200 ms; this minimum peak current for a 200 ms train is termed I_{200}. It should be recognized that a cerebral stimulus with intensity of I_{200} and with TD of 200 ms produces the same near-threshold subjective experience as does one with TD of 500 ms at the somewhat lower, liminal I current (*see* I-TD relationship; Libet *et al.*, 1964; Libet, 1966, 1973). The difference is that the 200 ms stimulus train obviously becomes adequate earlier than does the 500 ms one.

The minimum TD was judged to be at least 200 ms only when reduction of TD to 150 ms produced flatly negative (as opposed to 'uncertain') responses in every test. There were thus often instances in which the adopted minimum TD (of 200 ms) produced an inconsistent and uncertain subjective response ('maybe something was there'), and when consistent and not uncertain responses ('I felt it even though very weak') might require minimum train durations of 300 ms or more. In order to retain positive responses, suitable for subjective timings during a series of trials, it was found necessary to employ a TD of 500 or 600 ms, rather than the minimum effective one of 200 ms for the intensity of I_{200}. The use of such cerebral *test stimuli* (peak current intensity of I_{200} but TD of 500 or 600 ms) would imply the following: (a) the test stimulus produces a conscious sensory experience that is somewhat stronger than threshold, and it lasts longer than one produced by a stimulus with I_{200} and TD of 200 ms (*see* Libet *et al.*, 1964); (b) the test stimulus however *cannot become adequate before at least a 200 ms portion* of the total train duration of 500 to 600 ms has elapsed. (With some 'bobbling' of threshold effectiveness some test stimuli might require up to about 300 ms for adequacy, as noted above.)

It was not possible to match precisely the temporal and spatial features of the P-induced sensations with those of the cerebrally-induced sensations. The peak current of the 0·2 to 0·5 ms pulse to the skin could be set so that the subjective intensity of its sensation roughly matched the relatively weak subjective sensory experience produced by the test cerebral stimulus. However, the peripherally-induced sensation was sharper both in its spatial localization and onset, as well as briefer in duration and different in quality. The area of subjective spatial referral for the cerebral test stimuli (whether at SI cortex, n.VPL or LM) was not only larger but, not uncommonly, it could shift to some degree in successive tests of a given series (*see also* Libet *et al.*, 1964). It was also not uncommon (for example, subject G.S. in Table 2) for each cerebrally-induced sensation to have a 'spreading' character, i.e., it could start in a given smaller referral area and quickly extend to a wider referral area before terminating. Subjects in fact reported feeling that it was distinctly easier to perceive and report timing orders for P_1-P_2 rather than for P_1-cerebral couplings; in accordance with this there was a greater scatter (degree of inconsistency of reported timings for the same coupling interval) for the subjective timing orders reported with P_1-cerebral couplings than with P_1-P_2 couplings. In addition, a less sharp onset for a cerebrally-induced sensory experience might tend to bias the reported timing order in the direction of this experience starting relatively later than its actual time of onset might warrant. It should be noted that, in tests in which the P stimulus is coupled with one in n.VPL or LM (as in Table 2), any such bias would alter the reports in a direction contrary to that predicted by our modified hypothesis (*see* Results and Discussion); that is, it would tend to weaken the support for the hypothesis. However, in tests coupling a P with a cortical (SI) stimulus, such a bias would operate in the same direction as the hypothetically predicted one, and could thus provide some measure of false support for this particular prediction.

The longer duration of the cerebrally-induced test sensation, and to a lesser extent the less sharp onset, can be roughly matched by the peripherally-induced one if a suitable train rather than a single pulse is applied to skin. (Intensity of the pulse train to skin is also adjusted so that subjective intensities of the two different sensations also match). For such peripheral stimulus trains, the (skin TD) = (total TD of the cerebral test stimulus) minus (min TD required by cerebral test stimulus); for example, with a cerebral stimulus employing a test TD of 500 ms but requiring a minimum TD of 200 ms, the TD for the peripheral stimulus should be 500 minus 200, i.e., 300 ms. (This assumes that the peripheral stimulus requires a negligibly small minimum TD; *see* Libet *et al.*, 1964; Libet, 1973, and below). This arrangement (*see* Table 2) in fact did make the duration of the two sensations (skin vs. LM stimulus) appear subjectively similar, and it seemed to reduce the inconsistency of reported timings.

Data Analysis

The useful data that could be obtained with a given subject were limited in amount and scope in most cases. The first part of the study, reported in Section I of Results, was carried out in the operating room, during second stage acute procedures in which therapeutic electrodes were inserted and used for treatment of dyskinesias in the awake, responsive patients (Feinstein, Alberts, Wright and Levin, 1960). A number of the earlier cases involved in Section III of the Results were also studied in the operating room. Most of the studies in Section III, however, were carried out in sessions outside the operating room, with patients in whom therapeutic procedures required the electrodes to remain implanted for approximately a week (Feinstein *et al.*, 1969). Even in this group of ambulatory but in-hospital patients the quality and number of the rather demanding experimental test series that could be achieved with each subject was limited by their condition (recovering from the intracranial implantation procedure and undergoing therapeutic procedures during the week); in most cases it was not feasible to evolve and employ a fully adequate and standardized experimental series of tests. The latter became more readily possible in only a few of a small group of patients, most recently available, in whom stimulating electrodes were chronically implanted in LM for treatment of intractable pain (Feinstein *et al.*, in preparation). Two of this group of patients, in whom the implanted electrodes were still retained with apparent therapeutic benefit after some two to four years, were alert, younger men (H.S., G.S.) whose pain was now generally under control and of negligible significance, and who were able to return and participate adequately in suitably complete experiments (*see* Table 2). Even under optimal conditions, however, the total number of suitable trials in a given session of a few hours is limited by the nature of the subject's task in the experiment. The required attention to very weak sensory experiences itself imposes a considerable 'information load' (*see* e.g., Desmedt and Robertson, 1977); in the present experiments the weak and brief sensations induced by the cerebral test stimuli were even more elusive and required greater concentration by the subject than did the weakest effective peripheral stimuli. In addition, there was the task of remembering and reporting the temporal order for two experiences closely coupled. Even our normal subjects, who had to deal only with coupled peripheral stimuli, found each session somewhat demanding, and the total number of trials were kept to a minimum for best results (*see* Table 1). Therefore, statistical evaluation of results under even the best obtainable conditions required development of a statistical procedure that could deal successfully with the relatively small numbers both of different time intervals (for coupled stimuli) and of trials at each time interval. The statistical treatment was developed by Dennis Pearl, in consultation with Prof. Elizabeth Scott of the Department of Statistics, University of California at Berkeley; a discussion of the treatment is given below in connection with the data in Tables 1, 2, and 3. For the large number of other subjects, we had to rely on in-depth evaluation of more limited data in each case to make qualitative judgments of what such data appeared to demonstrate.

RESULTS AND DISCUSSION

I. *Subjective Timing Order for Couplings of a Threshold Peripheral Stimulus (P) with a Liminal Cortical (C) Stimulus Train*

When train duration of a cerebral stimulus with liminal intensity is reduced by 10 to 20 per cent below the average value of about 500 ms for the minimum or 'utilization' train duration (U-TD), the subject reports with certainty that he feels nothing (Libet *et al.*, 1964, 1972). It seemed justifiable, therefore, to assume that the conscious experience for a liminal C stimulus could not begin before the end of the U-TD, though it might begin afterwards (*see* fig. 1). The end of the U-TD is an empirically determinable value for a given subject. Consequently, the onset of the conscious sensory experience elicited by the liminal C stimulus appeared to be utilizable as a 'reference' time. The timing of a peripherally-induced sensory experience might then be meaningfully compared to the 'reference' time provided by the onset of such a cortically-induced sensation. (It should be recalled that conduction delays for the arrival of the peripherally-initiated neural message at the sensory cortex are trivial, in the context of the hundreds of milliseconds required for the 'reference' stimulus at cortex. The latency for the primary evoked potential, recorded on SI cortex in response to a stimulus on the hand, is about 15 ms or so).

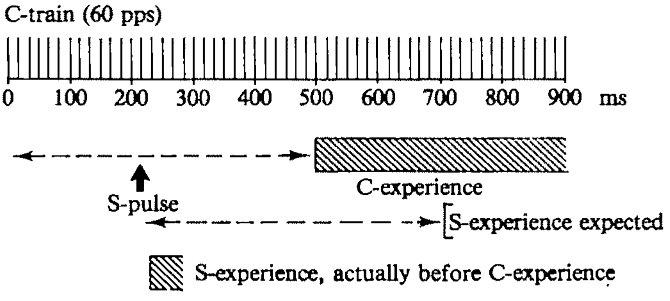


FIG. 1. Diagram of experiment on subjective time order of two sensory experiences, one elicited by a stimulus train to SI cortex (C) and one by a threshold pulse to skin (S). C consisted of repetitive pulses (at 60 pps) applied to postcentral gyrus, at the lowest (liminal) peak current sufficient to elicit any reportable conscious sensory experience. The sensory experience for C ('C-experience') would not be initiated before the end of the utilization-train duration (U-TD, average about 500 ms), but then proceeds without change in its weak *subjective* intensity for the remainder of the applied liminal C train (*see* Libet *et al.*, 1964; Libet, 1966, 1973). The S-pulse, at just above threshold strength for eliciting conscious sensory experience, is here shown delivered when the initial 200 ms of the C train have elapsed. (In other experiments, it was applied at other relative times, earlier and later.) If S were followed by a roughly similar delay of 500 ms of cortical activity before 'neuronal adequacy' is achieved, initiation of S-experience might have also been expected to be delayed until 700 ms of C had elapsed. In fact, S-experience was reported to appear subjectively before C-experience (*see* text).

On our original hypothesis (Libet *et al.*, 1964, 1972; Libet, 1966, 1973), a single pulse stimulus to the skin at just above threshold level should also be followed by a period of about 500 ms before cerebral neuronal adequacy for the conscious sensation would be achieved. If such a *skin pulse* (*S*) were to be applied some time (say 200 ms) *after* the beginning of the C stimulus train, then neuronal adequacy for the peripherally-induced sensation should be achieved after the end of the U-TD of the C train (in this example, at about 700 ms after the beginning of the C train; *see* fig. 1). If the *subjective experience* were to occur at the same time as the achievement of *neuronal adequacy* in the case of either stimulus, one would expect the subject to report that the conscious sensory experience for the C stimulus began before the appearance of that for the threshold S pulse (fig. 1).

Actual tests of this kind, with S delayed for variable times after the start of the C train, were carried out with six patients. In each of these subjects only a limited number of observations could be made. However, the pooled reports were predominantly those of sensory experience for the C (cortical) stimulus beginning *after*, not before, that for a delayed threshold S pulse; this was true even when the delivery of the S pulse was delayed from the start of the C stimulus train by almost the full value of the U-TD (that is, by up to 400 to 500 ms when U-TD was 500 ms). These findings indicated that the subjective experience of the skin stimulus occurs relatively quickly after delivery of the S pulse, rather than after the expected delay of up to about 500 ms for development of neuronal adequacy following the S input.

Study of this point in this way was carried out chiefly at a time (before 1969) when chronic implantations of therapeutic electrodes were not being made. Thus, only a relatively small number of tests could be made during the surgical procedure (with local anæsthesia) in the operating room, with each of the 5 subjects involved (4 parkinsonians, 1 spasmodic torticollis). A sixth subject, an amputee being treated for intractable pain in 1970, was tested via implanted electrodes outside the operating room. However, the results were qualitatively consistent among the different cases in this group.

II. *Modified Hypothesis, to Relate Subjective Timing to the Timing of Neuronal Adequacy for an Experience*

There were now two possible alternative conclusions that might be drawn from the experimental result in Section I, above. Alternative (1): the substantial delay empirically required to achieve neuronal adequacy with the cortical stimulus might not apply to the case of a sensory experience elicited by a peripheral stimulus. However, our previous evidence strongly supported the hypothesis of such a cerebral delay for eliciting even a peripherally-induced sensation (Libet *et al.*, 1972; Libet, 1973), and it argued against adopting this alternative (*see also* General Discussion). Alternative (2): there is a discrepancy between the subjective timing (of a conscious sensory experience) and the expected time at which 'neuronal adequacy' for eliciting the experience is achieved. In considering the apparent paradox posed by alternative (2) it was necessary to recognize that the original hypothesis dealt directly only with the time to achieve the *adequate neuronal state* that elicits the experience. The two timings, for subjective experience vs. neuronal adequacy, might not necessarily be identical. But if there were a discrepancy between the two kinds of timings, why should it appear in the case of peripheral skin stimuli and not with a cortical stimulus? A possible answer to this question lay in the difference between the initial cortical responses elicited by peripheral vs. cortical stimuli. The S (skin) pulse leads to a volley in the ascending specific projection (lemniscal) system; the latter elicits a relatively localized 'primary' (initially surface-positive) evoked potential in the SI cortex, with an onset latency of about 15 ms after a stimulus to the hand (*see*, Fig. 2; *see also* Jasper, Lende and Rasmussen, 1960; Desmedt, 1971; Goff, Matsumiya, Allison and Goff, 1977). The liminal C stimulus, applied subdurally at SI cortex (postcentral gyrus), does not elicit a similar type of response (*see* Libet *et al.*, 1967, 1972; Libet, 1973). With these considerations in mind we developed the following postulates, to be added as modifiers to our original hypothesis on the cortical processing time for a conscious sensory experience:

(1) Some neuronal process associated with the early or *primary evoked response*,

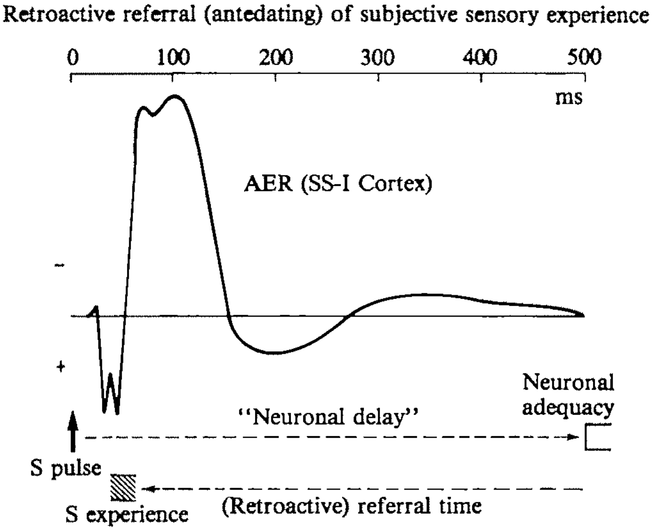

Retroactive referral (antedating) of subjective sensory experience

FIG. 2. Diagram representing the 'averaged evoked response' (AER) recordable on the surface of human primary somatosensory cortex (SI), in relation to the modified hypothesis on timing of the sensory experience. Below the AER, the first line shows the approximate delay in achieving the state of 'neuronal adequacy' that appears (on the basis of other evidence) to be necessary for eliciting the sensory experience. The second line shows the postulated retroactive referral of the subjective timing of the experience, from the time of 'neuronal adequacy' backwards to some time associated with the primary surface-positive component of the evoked potential. The primary component of AER is relatively highly localized to an area on the contralateral postcentral gyrus in these awake human subjects, as had been shown in anæsthetized patients (Jasper, Lende and Rasmussen, 1960). The secondary or later components, especially those following the surface negative component after the initial 100 to 150 ms of the AER, are wider in distribution over the cortex and more variable in form even when recorded subdurally (*see*, e.g., Libet *et al.*, 1975). It should be clear, therefore, that the present diagram is not meant to indicate that the state of 'neuronal adequacy' for eliciting conscious sensation is restricted to neurons in primary SI cortex of postcentral gyrus; on the other hand, the primary component or 'timing signal' for retroactive referral of the sensory experience would be a function more strictly of this SI cortical area.

The AER shown here is a composite drawing, based on actual recordings by us in several unanæsthetized patients, in whom a subdural metal contact was located on the pia-arachnoid surface of the postcentral gyrus (SI cortex) at a 'good spot'; the latter was defined by the low intensity required by a direct cortical stimulus train at this site in order to elicit a relatively localized somatic sensation (*see* Libet, 1973; Libet *et al.*, 1964), and by the fact that stimulation of another contact, located 5 to 10 mm anterior to it, could elicit the localized pyramidal-type motor response typical with primary motor cortex. In each case the evoked potentials were recorded (relative to an indifferent electrode usually on ear lobes) in response to single pulse stimuli (S). The latter were applied to a contralateral area of skin within the referral area for the sensation elicited when stimulating via the recording SI cortical electrode. Skin stimuli were just above the threshold for eliciting a sensation in 100 per cent of the trials. The AER for each subject was the average of SI evoked potentials from usually 256 such stimuli, delivered at about 1/s. (The later components of these AERs are probably relatively minimal in their amplitudes, compared to what could presumably be obtained if the rate of stimulus repetition were lower than 1/s and if the subjects had been asked to perform some discriminatory task in relation to the series of 256 stimuli, as in Desmedt (1971). The composite form of these AERs to skin stimuli may be compared with those obtainable as responses to stimulating the median nerve, both with intracranial recordings (Hirsch, Pertuiset, Calvet, Buisson-Ferey, Fischgold and Scherrer, 1961) and with scalp recordings (*see*, e.g., Desmedt, 1971; Goff, Matsumiya, Allison and Goff, 1977)).

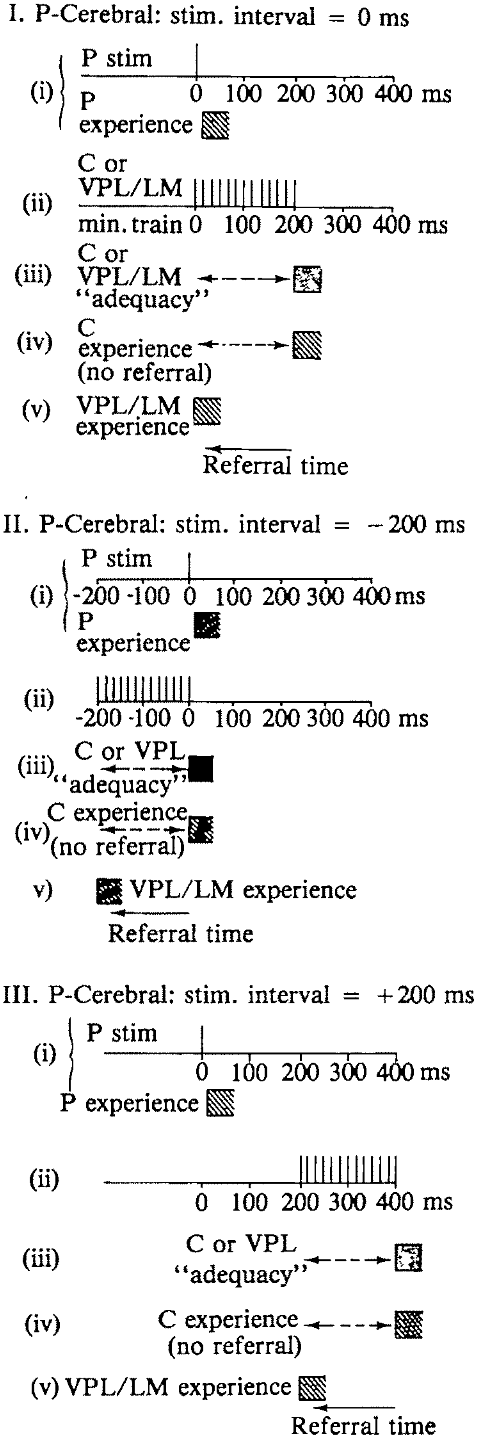
of SI (somatosensory) cortex to a skin stimulus, *is postulated to serve as a 'time-marker'*. (2) There is an automatic *subjective referral of the conscious experience backwards in time* to this time-marker, after the delayed neuronal adequacy at cerebral levels has been achieved (*see* fig. 2). The sensory experience would be 'antedated' from the actual delayed time at which the neuronal state becomes adequate to elicit it; and the experience would appear subjectively to occur with no significant delay from the arrival of the fast projection volley. Fortunately, it was possible to put these newly added postulates to experimental tests that could potentially falsify them.

Predictions from the hypothesis. The chief test of the modified hypothesis was based on the unique conditions associated with a cerebral stimulus applied to LM or n.VPL, as contrasted with one to SI cortex. As already noted, a stimulus applied to LM or n.VPL requires the same kinds of minimum train durations as one applied to SI cortex, in order to elicit a conscious sensory experience. However, unlike SI cortex, each volley in LM or n.VPL should and does elicit a primary evoked response in SI cortex equivalent to the early components in the response to a skin pulse, which are seen in fig. 2 (Libet *et al.*, 1967). The primary cortical response to an LM volley should supply the same putative timing signal as does the single skin pulse. Consequently, the modified hypothesis would lead to a startling prediction: the subjective timing of a sensory experience elicited by a stimulus train in LM (or n.VPL) should be essentially similar to that for a skin pulse (i.e., as if there were no perceptible delay from the onset of the LM train); this should occur in spite of the experimental fact that the stimulus to LM or n.VPL does not become adequate until its train duration has achieved a substantial value of up to about 500 ms, depending on the intensity employed.

A diagram of the experimental paradigm for these tests with pairs of temporally-coupled stimuli is shown in fig. 3. For the cerebral stimulus train at 60 pps, whether cortical (C) or subcortical (LM or n.VPL), the intensity (peak current per pulse) is adjusted so that a minimum train duration of about 200 ms is required in order to elicit any conscious sensory response (*see* Methods).

FIG. 3. Diagram of timing relationships for the two subjective experiences when a peripheral stimulus (P) is temporally coupled with a Cerebral stimulus, as predicted by the modified hypothesis. The Cerebral stimulus train is located either at SI cortex (C) *or* in n.VPL (or LM). Therefore, timing relationships may be compared for two types of coupled pairs: (a) P paired with SI; and (b) P paired with n.VPL/LM. In set I, the *time interval* between (i) P stimulus and (ii) *onset* of a cerebral train (whether C or VPL/LM) = 0; in set II, this interval = −200 ms (i.e., cerebral stimulation starts 200 ms before P); in set III, the interval = +200 ms.

P usually consisted of a single pulse applied to skin of the hand (but trains used for experiments in Tables 1 and 2) on the side of body opposite to that in which a referred sensation was elicited by the cerebral stimulus. The P-experience (*see* (i)) is timed subjectively to appear within 10 to 20 ms after the P stimulus (*see also* fig. 2). Each cerebral stimulus (in (ii)) is a train of pulses, usually 60 pps, with peak current adjusted so that a minimum train duration of about 200 ms is required in order to produce any conscious sensory experience; this means that the state of 'neuronal adequacy' (*see* (iii)) with either C or VPL/LM stimuli could not be achieved before 200 ms of stimulus train duration had elapsed. The subjective timing of the experience of C stimulus (iv) should be delayed for a time similar to this minimum TD of 200 ms. But the experience of VPL/LM(v) should be timed earlier; i.e., it should be subjectively referred retroactively, to a time associated with the primary evoked cortical response that is elicited even by the first pulse of a stimulus train in the VPL/LM portion of the specific projection pathway.


I. P-Cerebral: stim. interval = 0 ms
(i)
P stim
P experience
0 100 200 300 400 ms
(ii)
C or VPL/LM
min. train 0 100 200 300 400 ms
(iii)
C or VPL/LM
"adequacy"
(iv)
C experience
(no referral)
(v)
VPL/LM experience
Referral time
II. P-Cerebral: stim. interval = −200 ms
(i)
P stim
-200 -100 0 100 200 300 400 ms
P experience
(ii)
-200 -100 0 100 200 300 400 ms
(iii)
C or VPL
"adequacy"
(iv)
C experience
(no referral)
v)
VPL/LM experience
Referral time
III. P-Cerebral: stim. interval = +200 ms
(i)
P stim
0 100 200 300 400 ms
P experience
(ii)
0 100 200 300 400 ms
(iii)
C or VPL
"adequacy"
(iv)
C experience
(no referral)
(v) VPL/LM experience
Referral time

For *P-Cerebral stim. interval* = *0* (fig. 3-I). When a P stimulus pulse or train (to skin or nerve) and a stimulus train to LM (or n.VPL) are begun synchronously (i) and (ii), the patient should report that the *subjective* onsets of both conscious experiences are very close together or synchronous (i) and (v). This should occur even though it is empirically established that stimulus adequacy for the LM/n.VPL stimulus cannot become adequate until after its minimum TD of 200 ms has elapsed, while the P stimulus is adequate either after 1 pulse, or within 33 ms or less when a train is used to elicit a sensation matching both the subjective intensity and duration of the LM-induced one (*see below*). *Neuronal adequacy* for the experience (as distinguished from stimulus adequacy for inducing this neuronal response) would be achieved after a roughly similar delay for both LM and P (as well as for C), as in fig. 3-I (iii) and in fig. 2, according to the hypothesis. On the other hand, with a similar coupling between P and C stimuli, sensory experience for C should be reported to appear after that for P (i) and (iv), as in experiments of Section I above. This should occur even though it is empirically established that C stimulus becomes adequate after the same minimum TD of 200 ms as does LM stimulus.

For *P-Cerebral stim. interval* = *−200 ms* (fig. 3-II). When LM/n.VPL stimulus train is begun 200 ms before P stimulus (ii) vs. (i), the patient should report that the experience for LM/n.VPL starts before that for P (i) and (v); whereas for a similarly coupled C stimulus the onset of the experience should be reported to come either at the same time or possibly after that for P (i) and (iv).

For *P-Cerebral stim. interval* = *+200 ms* (Fig. 3-III). When cerebral stimulus train is begun 200 ms after P stimulus (ii) vs. (i), patient should report that the experience for either LM/n.VPL or C stimuli (v) and (iv) appears after that for P (i).

III. *Subjective Timing Orders, Experimentally Determined, for Couplings of P_1-P_2, P_1-LM, and P_1-C*

A. *Couplings of two peripheral stimuli* (P_1-P_2). In order to assess the significance of the relative subjective timings for couplings of peripheral and cerebral stimuli, it is necessary to have an appropriate 'control' series in which the cerebral stimulus is replaced by another suitable peripheral one (P_2). Indeed, the experimental question becomes one of directly comparing the reported timing orders for a block of trials with P_1-P_2 couplings with those for a block of trials with P_1-cerebral couplings (both types of pairings temporally-coupled by similar intervals). Any *difference* between the two sets of subjective timing orders (for P_1-P_2 vs. P_1-cerebral couplings) would indicate the presence or absence of a delay in subjective timing for the cerebral stimulus relative to a comparable peripheral one (*see* Tables 2B and 3B). In this method each subject provides his own individual control or comparison data, in the patterns of his reports of subjective timing orders for two peripheral stimuli which should be processed with no differences which are significant in the present context.

Skin stimulus trains which elicit a sensation matching the subjective intensity and duration of that induced by the test cerebral stimuli (*see* Methods) were found to be below the threshold I for a single pulse and to require a minimum TD of 17 or 33 ms, that is, 2 or 3 pulses at 60 pps. When such an S train is coupled with an LM stimulus train which has a minimum requirement of 200 ms TD, the difference between the required stimulus durations for S vs. LM could, therefore, be reduced from 200 ms down to 167 ms. The possible impact of such a 33-ms reduction in the effective coupling intervals, on the pattern of reported subjective timing orders, was tested in normal subjects (Table 1).

In these, the P_1–P_2 stimuli were applied to skin of the right and left hands respectively, becoming S_R (right) and S_L (left) stimuli. Stimulus intensity in each case was reduced to a level that required a minimum of 2 or 3 pulses at 60 pps (TD = 17 or 33 ms) to elicit any sensory experience; but actual TD of each test stimulus was 300 ms, to simulate both the subjective intensity and duration of cerebrally-induced sensations (*see* Methods). For the A-blocks of trials, S_R–S_L coupling intervals ranged from −200 to +200 ms (and were similar to the 'control' series with S_1–S_2 couplings in Table 2). For the 'experimental' B-block series in Table 1, delivery times of S_R stimuli were modified by delaying onset of each S_R stimulus by 33 ms. This reduced each S_R–S_L coupling by 33 ms, from what the interval had been in the first or A series of the session with that subject; for example, an S_R–S_L interval of −200 ms (that is, S_R started 200 ms after S_L) in series A would now become −233 ms in B, while an interval of S_R–S_L = 0 (synchronous delivery) in A would now become −33 ms (S_R started after S_L) in B, etc. In all Tables the value of the coupling time interval between test pair of stimuli was varied in a random manner in successive trials. However, all the subjects' reports in those trials using a given coupling time interval in a given block of trials are collected together in the Table under 'Subject's timing'. In block A of Table 1, for example, subject D.A. was presented with an S_R–S_L interval of 0 in 10 trials which were randomly distributed among the total of 50 trials in block A. Of these 10, she reported experiencing S_R (skin of right hand) 'first' in 3 trials; she reported S_R and S_L sensations starting 'together' (T) or at the same time in 7 trials; and there were no reports of 'S_L first' in any of these 10 trials.

The comparison of timing orders in block A with those in block B trials of Table 1 simulates the design for the experiments in Tables 2 and 3. But in Table 1 the known delay imposed on one of the stimuli (S_R in block B) should theoretically produce a similarly defined shift in subjective timing of the sensation elicited by that stimulus; whereas in Tables 2 and 3 the possibility of a shift in subjective timing relative to onset of a stimulus train in LM or SI cortex constitutes the unknown point. Therefore, the experiment in Table 1 serves as at least a partial check on the validity of this design and of the statistical method employed in the analysis, as well as to test the specific question of what effect a 33-ms shift may have on overall pattern of reports of subjective timing.

Comparing block A with block B for each subject in Table 1A, it is seen that the extra 33-ms delay for S_R stimuli produced no change in subjective timing orders for the 200- and 150-ms coupling intervals (that is, the orders remained essentially the same as the actual order of stimuli delivered). However, small differences between blocks A and B did appear for shorter S_R–S_L intervals; these indicated qualitatively that in series B there was a slight shift of reported timing orders in the expected direction of a small delay in the experience of S_R relative to that

TABLE 1A. SUBJECTIVE TIMING ORDERS OF EXPERIENCES FOR TEMPORALLY-COUPLED PAIRS OF SKIN STIMULI, RIGHT VS LEFT HANDS, IN NORMAL SUBJECTS

				Subject's timing			*Estim.*	
Subject		*S_R–S_L interval (ms)*	*No. of trials*	*S_R first*	*T*	*S_L first*	*Estim. 'mean shift' (ms)*	*Approx. SD*
D.A. (female, aged 26 y)	A	−200	10	0	0	10		
		−100		0	3	7		
		0		3	7	0	−30	10
		+100		10	0	0		
		+200	↓	10	0	0		
	B	−233	10	0	0	10		
		−133		0	1	9		
		−33		0	10	0	18	16
		+67		8	1	1		
		+167	↓	10	0	0		
R.J. (male, aged 29 y)	A	−200	10	0	0	10		
		−100		0	0	10		
		0		0	3	7	100	21
		+100		3	6	1		
		+200	↓	8	1	1		
	B	−233	10	0	0	10		
		−133		1	0	9		
		−33		0	1	9	122	25
		+67		2	7	1		
		+167	↓	6	3	1		
J.Wl. (male, aged 31 y)	A	−200	6	0	1	5		
		−150		0	0	6		
		−100		0	0	6		
		−50		1	0	5		
		0		2	1	3	−5	14
		+50		5	1	0		
		+100		6	0	0		
		+150		6	0	0		
		+200	↓	6	0	0		
	B	−233	6	0	0	6		
		−183		0	0	6		
		−133		0	0	6		
		−83		1	1	4		
		−33		1	0	5	22	14
		+17		4	0	2		
		+67		6	0	0		
		+117		6	0	0		
		+167	↓	6	0	0		

Effect of added 33 ms delay for one stimulus of each pair, *see* text.

Table 1b. Comparison of Timing Orders for Two Blocks of S_R-S_L Pairs, when One Block of Stimulus Coupling Intervals is Shifted by 33 ms.

Subject	*Comparison*	*Estim. change in shift (ms)*	*Approx. SD*	*Approx. 95% confidence interval*
D.A.	A vs. B	−48	19	(−86; −9)
R.J.	A vs. B	−22	33	(−87; 43)
J.Wl.	A vs. B	−27	20	(−68; 13)
	$(S_R-S_L)_A-(S_R-S_L)_B$			

for S_L. Statistical evaluation of the data in Table 1 was carried out by the same procedure that was developed for treatment of experimental data obtained with the patients, as in Tables 2 and 3 (*see* discussion of statistical terms, etc.). The 'mean shift', in the subjective timing for S_R relative to S_L, should be close to 0 for each A-block, since the coupling intervals are grouped symmetrically, + and −, around 0. (In fact, however, the mean shift was close to 0 only for subject J.Wl.; the −30 ms shift for D.A. indicates a slight 'bias' in the direction of reporting S_R first, and the +100 ms shift for R.J. indicates a bias in the opposite direction. All three subjects were right-handed).

The *change in mean shift*, when block B (S_R delayed by 33 ms) is compared with block A, is given for each subject in Table 1b. The changes in mean shift are not far from −33 ms for all three subjects; the changes all indicate a statistical tendency to experience S_R as delayed, relative to S_L, by a time not far different from the actual delay imposed on S_R' in the S_R-S_L couplings in block B.

Statistical treatment. In this treatment, the responses for all the stimulus-coupling intervals in a given series or block of trials are used to estimate a 'mean shift'. The mean shift is, qualitatively speaking, the best time delay to use for one of the stimuli in order to get close to the centre around which the subject is reporting the relative orders for the other stimulus in all the temporally-coupled pairs in that block. (A value of zero for the mean shift would indicate no shift, in the subjective timing 'centre' of the first stimulus relative to the second stimulus of each pair, from the actual relative positions of the coupled stimuli as delivered. A negative value for the mean shift indicates that subjective timing 'centre' for the first stimulus of the pair is shifted retroactively away from the timing for the second; that is, the timing for the second stimulus is delayed from that of the first by this value).

The *difference* between the mean shifts for two blocks of trials, carried out in the same or in a closely comparable session, gives the estimated change in shift. For each such change in shift, the standard deviation (SD = square root of the variance) and the approximate '95 per cent confidence interval' is given. The latter consists of two values (in parentheses, Tables 1b, 2b, 3b) each of which is equal to two standard deviations on either side of the estimated change in shift; that is, we are about 95 per cent certain that the true value of the change in shift lies between these two values. The estimated 'change in shift' in the appropriate direction for all three subjects (Table 1b) is surprisingly close to the relatively small imposed shift of 33 ms, and it provides a kind of confirmatory test of the validity of the statistical procedure.

In Tables 2 and 3, of course, the comparisons for change in shift are between a block of trials for P_1–P_2 couplings and a block of P_1-cerebral couplings ('cerebral' stimuli being those to LM in Table 2, and to SI cortex in Table 3). When P_1 is common to both blocks, the change or difference in mean shifts between the two blocks reflects the difference between subjective timings for the second stimuli of the couplings in each block, for example, between the timings for S_L and for C (*see* Table 3B). When the mean shift for block B is subtracted from that for block A, a positive value for the resulting 'change in shift' indicates a delay for timing of the second stimulus in block B (C in Table 3B) relative to the timing for the second stimulus in block A (S_L in Table 3B).

A fuller, rigorous description and analysis of the statistical treatment is beyond the scope of the present paper. An alternative statistical approach which could have been adapted to our needs has since been published (Dempster, Laird, and Rubin, 1977). Three assumptions involved in formulating the statistical model employed were as follows: (i) for a particular block of data the shift function is roughly constant from trial to trial, and (ii), each trial is independent. Both of these assumptions appear to be reasonable and warranted on the basis of the care taken to maintain constant conditions within a given session, keeping the total load on the subject at levels well below any apparent fatiguability, etc., and randomizing the presentation of the coupling time intervals in successive trials; in addition, data of the exact sequence of responses were examined for subjects H.S. and G.S. in Table 2, and they showed no significant deviation from the assumption of independence of trials; (iii) the distribution function of the responses is roughly linear within the experimental range even for coupling time intervals which were not tested, and also for the range of intervals extending where necessary on either side of the experimental range. This assumption introduces a possible 'interpolation error'. This potential error tends to be reduced by the use of more different time intervals for coupling, for example, at least five intervals for the series in Tables 1 and 2 instead of the three employed in most of our other experiments. The probable actual interpolation error, due to linearizing the estimated shift function, appeared to be no more than 10 ms in the experiments using five different time intervals (as in Table 2A) and no more than 30 ms in experiments using three. Fortunately, the amounts in such errors would not seriously affect the significance of the data in relation to the hypothesis being investigated.

'Accuracy' of timing orders for paired peripheral stimuli. The degree of 'accuracy' (the similarity of the reported to the actually applied order of P_1–P_2 stimuli) had to be virtually 100 per cent for P_1–P_2 coupling intervals of 200 ms, in order to be useable for the comparisons with the P_1-Cerebral couplings. Experimental tests of the hypothesis required that the subject be capable of subjectively distinguishing timing orders for intervals equal to or less than the minimum TD of 200 ms that was required by the test cerebral stimuli. Fortunately, subjective timing orders for S_R–S_L coupling intervals of 200 ms did turn out to be essentially 100 per cent 'accurate' for almost all the patients tested. The 'accuracy' was often somewhat reduced with 150-ms intervals, and distinctly poorer with 100-ms intervals (for which some patients could not report consistent orders). The examples in Tables 2 and 3 illustrate this point. The use of brief trains of pulses (300 to 400 ms TD's) for skin stimuli, rather than the single pulse stimuli used in most of the subjects, did not appear to affect the reported timing orders.

The foregoing was also applicable to 'normal' subjects (non-patients); some of these exhibited considerable 'accuracy' even with a 50-ms interval, but almost none with a 25-ms interval. Four normal subjects with ages in the 40's and 50's were tested with single pulse S_R and S_L stimuli. In 4 subjects the S stimuli were trains of weak pulses to better simulate the cerebrally-induced sensations (data for 3 of these are given in Table 1A, with similar results for the fourth, a female aged 40 years). The weaker S-induced sensations in this second group appeared to be more demanding of effort and alert attention by the subjects; indeed, in two additional subjects who were studied at the end of their regular eight-hour working period as nurses, the reported timing orders for given coupling intervals exhibited considerable variability and the 'accuracy' was poor. This factor probably helps explain some of the inconsistency of results obtained with P_1-Cerebral couplings in the patients; most of the patients were not in an optimal physical and mental state when they were studied with P_1-Cerebral trials in which the cerebrally-induced sensation was always, because of the experimental requirements, similarly weak in subjective intensity.

Negative 'mean shifts' for S_1-S_2 in Table 2A. For subject H.S., blocks A and C, estimated 'mean shifts' are −41 and −91 ms respectively; for subject G.S., block A, it is −35 ms even though the left-right order is reverse of that for H.S. The mean shifts for comparable blocks of trials were −21 and −9 ms for patients J.W. and C.J. in Table 3A; and −30, +100, and −5 ms for the normal subjects in Table 1A. To the extent that the negative shifts in Table 2A may be significant, they would imply that, for these patients, a stimulus to skin on the normal side (S_L for H.S., and S_R for G.S.) tended to be subjectively timed somewhat earlier than a comparable stimulus on the abnormal side (that was treated for pain). Most of this estimated negative mean shift appears to be associated with an asymmetry between the responses for the smaller time intervals, that is, for −100 ms (or −150) compared to those for +100 ms (or +150 ms). For both subjects, the reported timing orders were predominantly S_1 and S_2 'together' for the −100 (−150) ms intervals; whereas, they were predominantly 'S_1 first' for the +100 (+150) ms intervals, in accord with the actual order of delivery. This asymmetry is in fact associated with a modest but definite deficit in epicritic sensibilities on the abnormal side (right side for H.S., and left for G.S.). The deficits are ascribable to losses in the specific projection pathway probably at thalamic levels, due either to their own pathological disorders, or to small heat lesions in n.VPL or just subthalamic sites (which were made to treat their pain some years prior to implanting the present stimulating electrodes in LM), or to both. The results obtained for S_1-S_2 couplings when both stimuli were located on the normal side in subject G.S. (Table 2A, block D) are in accord with this interpretation; the smaller estimated mean shift of −19 ms has a standard deviation of ±14 and the designation of + vs. − direction was an arbitrary one in block D, in which either of the S stimuli could have been called S_1. For the S_{normal}–$S_{abnormal}$ couplings in these patients, negative mean shifts are in fact explainable by our modified hypothesis; if a small deficit in specific projection pathway were present on one side, the reduction in putative early 'timing signal' delivered by this system to the cerebral cortex should tend to reduce the degree of retroactive subjective referral of the timing for that abnormal side.

B. *Couplings of a peripheral stimulus (P_1) with a medial lemniscus stimulus (LM).* The technically most satisfactory experimental series of this type are presented in Table 2 (*see further details* in small print section below). They were carried out with two subjects (H.S. and G.S.) who were able to return for study a few years after the permanent implantation of electrodes in LM. (The implantation was made for the therapeutic relief of intractable pain of central origin by self-stimulation (Feinstein *et al.*, in preparation). The subjects were now outpatients with their pain controlled and presenting no interference to studies. They were in relatively good physical and psychological condition, and they were able to tolerate well a more concentrated period of successive morning and afternoon study sessions for two days each. Peripheral stimuli were matched in the best obtainable manner to the LM stimuli (*see* Methods). The experiments could be designed and completed in a manner making them as amenable to statistical evaluation as were the experiments with the normal subjects (in Table 1).

The distribution of reported subjective timing orders is seen in Table 2A to be roughly similar for both the S_1-S_2 and the S_1-LM couplings. For example, with a coupling interval of −200 or −250 ms for either S_1-S_2 or for S_2-LM pairs, most or all the reports were either 'S_2 first' or 'LM first' respectively, as seen in the appropriate blocks. If the subjective timing for LM had actually been delayed an extra 200 ms, in accordance with the minimum TD requirement of 200 or more ms for the LM stimulus employed, one would have expected that the S_1-LM couplings

TABLE 2A. SUBJECTIVE TIMING ORDERS OF EXPERIENCES FOR TEMPORALLY-COUPLED STIMULI: COMPARE SKIN (S_1) AND MEDIAL LEMNISCAL (LM) PAIRINGS WITH S_1-S_2 PAIRINGS

		LM stim.					*Subject's timing*				
Subject		*Min. TD* (*ms*)	*Test TD* (*ms*)	*S_1-S_2* / *S_1-LM*	*Interval* (*ms*)	*No. of trials*	*S_1 first*	*T*	*S_2/LM first*	*Estim. 'mean shift'* (*ms*)	*Approx. SD*
H.S. (male, aged 62 y)	A			S_L-S_R	−200	9	0	1	8	−41	9
					−100	9	0	8	1		
					0	10	0	10	0		
					+100	11	9	2	0		
					+200	10	10	0	0		
	B	200-300	600	S_L-LM	−200	10	0	0	10	1	18
					−100	↓	1	6	3		
					0	↓	1	9	0		
					+100	↓	1	8	1		
					+200	↓	10	0	0		
	C			S_L-S_R	−250	5	0	0	5	−91	23
					−150	6	1	3	2		
					0	5	0	4	1		
					+150	5	5	0	0		
					+250	5	5	0	0		
	D	300	600	S_L-LM	−250	6	0	0	6	−109	39
					−150	4	1	0	3		
					0	4	0	4	0		
					+150	5	3	2	0		
					+250	5	5	0	0		
G.S. (male, aged 57 y)	A			S_R-S_L	−200	10	0	0	10	−35	8
					−100	11	0	10	1		
					0	10	0	10	0		
					+100	10	8	2	0		
					+200	10	10	0	0		
	B	200	500	S_R-LM	−200	8	0	2	6	−25	25
					−100	8	0	8	0		
					0	9	4	2	3		
					+100	7	4	2	1		
					+200	10	8	1	1		
	C	200-300	500	S_R-LM	−200	10	0	4	6	−12	28
					−100	↓	0	8	2		
					0	↓	2	6	2		
					+100	↓	6	3	1		
					+200	↓	8	1	1		
	D			S_1-S_2 (both on R. side)	−200	9	0	1	8	−19	24
					−100	11	0	4	7		
					0	10	2	7	1		
					+100	10	8	2	0		
					+200	10	10	0	0		

TABLE 2B. COMPARISONS OF TIMING ORDERS FOR (S_1-S_2) VS. (S_1-LM)

Subject	*Min. TD for LM (ms)*	*Comparison*	*Estim. 'change in shift' (ms)*	*Approx. SD*	*Approx. 95% confidence interval*
H.S.	200–300	A vs. B (S_L-S_R)—(S_L-LM)	−42	20	(−82; −2)
	300	C vs. D	18	46	(−74; 110)
G.S.	200	A vs. B (S_R-S_L)—(S_R-LM)	−10	26	(−63; 43)
	200	A vs. (B+C)	−30	24	(−78; 18)

at −200 ms should have produced more reports of 'together' (both sensations experienced about the same time) or even of 'S_1 first'.

This qualitative impression of overall similarity between the subjective timing orders for S_1–S_2 vs. S_1–LM couplings is substantiated by the results of the statistical evaluation. The following should be noted in Table 2B: (a) each 'estimated change in mean shift' is relatively small, far less than the minimum TD of 200 ms or more required by the LM stimulus to elicit any sensory experience. Furthermore, most of the changes in shift are negative, although probably not significantly so. If valid, a negative change would indicate that subjective timing for LM is slightly earlier than, rather than delayed after, that for S_2 (each relative to S_1). (Such an earlier timing might even be additionally explainable by the shorter latency time for the primary cortical response to an LM volley than to an S volley, although there are other possible small modifiers in both directions); (b) the 95 per cent confidence intervals do not contain the value of the minimum TD of 200 ms or more that is required by the LM stimulus; consequently it is very unlikely that the data can be explained by a shift or delay in subjective timing equal to or determined by this minimum TD of the LM stimulus. Rather, the data are most reasonably explained on the basis of the prediction from the hypothesis, that subjective timing for an LM stimulus was roughly similar to that for a peripheral S stimulus, in spite of the empirically determined extra 200 ms or more that was required by the LM stimulus to be effective at all.

A much larger number of less adequate experimental series was carried out prior to those in Table 2 (*see* Methods). These included preliminary studies in four subjects, in which controls and experimental procedures were being developed. There were also previous extensive studies with H.S. and G.S. that were conducted under less favourable conditions than those in Table 2; these included 12 sessions with H.S., some five years earlier (during a prolonged stay of two and a half months in the hospital) plus a few sessions two years after that during a revisit, as well as 5 sessions with G.S. some two years earlier. Additionally, there were sessions of variable numbers and durations with two other patients with chronically implanted electrodes in LM. Our own in-depth analyses of each case convinced us that, when experimental conditions were at least partially adequate, the results obtained were qualitatively in support of the hypothesis, that is, they tended to show patterns of subjective timing qualitatively resembling those in Table 2.

In Table 2, the stimulus to LM (medial lemniscus) consisted of a train of 0·2 ms-pulses at 60 pps. Peak current intensity was set so that a minimum train duration (TD) of 200 or 300 ms was required (*see* 'min TD' column) in order for the stimulus to elicit any reportable sensory experience. The actual test stimulus applied to LM, in each trial with an S_1-LM coupling, was at this same intensity (I_{200}) but had a TD longer than the minimum required one (*see* values under 'test TD' column), and explanation in Methods). The peripheral stimuli, P_1 and P_2, were applied to the skin and are called S_1–S_2. Since the LM-induced sensation (that replaces S_2) was referred to the right side for subject H.S. and to left side for subject G.S., S_1 and S_2 were actually S_L and S_R, respectively, for subject H.S., but S_R and S_L, respectively, for subject G.S. Each test stimulus to skin (whether S_1 or S_2) consisted of a train of 0·2 ms-pulses, 60 pps, with peak current set so that subjective intensity of the sensation approximated that elicited by the test LM stimulus; and TD was set at 400 ms in block A for H.S. and at 300 ms in all the other S_1–S_2 blocks, so as to approximate the subjective duration of the sensation elicited by the LM test stimuli.

Reports of 'subject's timing' for either S_2 or LM 'first' refer, respectively, to whether a block of S_1–S_2 couplings or S_1–LM couplings is involved. In block D for G.S., S_1 and S_2 were both located on the normal right hand (S_1 on back of hand near digits 4–5, and S_2 on ventral aspect of wrist). *See* small print section above on 'Negative mean shifts . . .' for comparison of these results in block D with those in block A, S_R-normal side vs. S_L-abnormal. Because of this, it was not appropriate to compare blocks C and D for subject G.S. in the same way as the other comparisons in Table 2B. Instead, the two blocks with S_R-LM trials (blocks B and C) were combined and then compared to block A (S_R–S_L trials) for subject G.S. In any case, however, a comparison of the D vs. C blocks in subject G.S. in fact produces a result qualitatively similar to that for A vs. B.

C. *Couplings of a peripheral stimulus* (*P*) *with an SI cortical stimulus* (*C*). These experiments were similar in principle to those in section III-B above, but with the cerebral stimulus applied subdurally to somatosensory, SI cortex (C), rather than to LM. Blocks of trials with paired P_1-C stimuli were compared in each subject with blocks of P_1–P_2 stimuli, with coupling intervals for each trial that overlapped for the two blocks. P_1 was either a single pulse to the skin (S_1) of the hand opposite to that in which C-induced sensation was referred, or in many cases it was a brief but weak flash of light (F). P_2 was a single pulse to skin (S_2), usually placed within the referral area of the C-induced sensation. As with LM, the C stimuli (pulse trains, 60 pps) were set at intensities somewhat above liminal levels so that a *minimum* TD of at least 200 ms or more was required to elicit any sensory experience; and, with these same intensities, the *test* TD's used in the actual trials were longer than the required minimum (*see* actual values in columns under 'min TD' and 'test TD'). The results obtained with C trains of unidirectional cathodal pulses ('cath') were distinctly different from those with C trains of pulses that successively alternated or reversed in polarity ('PR'). The two kinds of P_1–C couplings are therefore considered separately.

In Table 3 subjects J.W., C.J., W.M. and A.E. were parkinsonians; subject O.K. had 'basal ganglion disease' and M.T. had spasmodic torticollis. The S_1 and S_2 stimuli were single pulses, whose intensities were matched subjectively but were at levels distinctly above the threshold. Therefore, unlike those in Table 2, the sensations elicited by these S stimuli were not optimally matched, for subjective intensity and duration, with the cortically-induced sensations. Subjects in Table 3 were inpatients who were less able, than those in Table 2, to maintain consistency of reported sensory experiences in a long series of trials when S stimuli were set very close to threshold intensities for a conscious sensory experience. The use of a suprathreshold single pulse for S stimuli could have to some unknown degree biased the reported subjective timing orders for S_1-C couplings in the direction of S_1 first. However, any such bias would appear not to have determined the qualitative overall pattern of timing orders, as illustrated by the following: in subject C.J., the same S stimuli produced quite different results for C-cathodal (block B) when compared to C-polarity reversed pulses (block C). On the other hand, the use of a weak flash of light in place of S_1 (in P_1-C couplings with C-cathodal) produced a pattern of subjective orders (subject M.T.) qualitatively similar to those using S_1 and C cathodal (as in J.W., C.J. and O.K.).

For subject O.K., S_R was applied to back of right hand, while the C-induced sensation (stimulus to left SI cortex) was referred to the same right side but to the vicinity of the ear. The coupling of this S_R (instead of S_L) with C would result in the processing of the initial responses to S_R and C at separate sites in the same, left postcentral gyrus. However, this did not prevent the subject from maintaining a clear distinction between the timings for the two sensations, as he reported a preponderance of 'S_R first' (in block B) compared to the reports for S_L-S_R couplings (in block A). It may be added that trials (in some other subjects) with S_1 and S_2 on the same side have generally produced timing orders with an 'accuracy' comparable to series using S_R and S_L analysis (for example, Section III, block D for G.S. in Table 2A). However, there tended to be less confusion and less effort required on the part of the subject with comparisons of one side vs. the other.

For Table 3B, 'changes in shift' were estimated only for those experiments in Table 3A in which stimulus C consisted of cathodal pulses.

1. *P_1-C couplings using a cathodal pulse train for C.* Results from those experiments in which suitable comparative blocks of trials were achieved are given for subjects J.W., C.J., O.K., and M.T. in Table 3A. Patterns of subjects' timing orders (blocks A vs. B in these subjects) show a qualitative difference from those in Table 2A (with LM stimuli). For example, J.W. reported in most of the trials with S_R-C interval at -300 ms (i.e., C stimulus train begun before S_R by 300 ms) that the S_R- and C-induced sensations subjectively started 'together'. But when two peripheral stimuli, S_R-S_L, were coupled by intervals of -200 and -150 ms he reported mostly 'S_L first'. Only when C stimulus was advanced to 400 ms before S_R (S_R-C interval $= -400$) did J.W. report mostly 'C firsts'. Similarly, with coupled stimuli initiated simultaneously (coupling interval $= 0$), J.W. reported mostly 'S_R first' for the S_R-C couplings, but mostly 'together' for the S_R-S_L couplings.

The statistical analysis of all the suitable data is in agreement with the impression of a qualitative difference. The estimated 'change in mean shift', when C stimulus (cathodal pulses) was substituted for the S_2 stimulus ('mean shift' for block A minus that for block B) is given in Table 3B for subjects J.W., C.J. and M.T. They all show values for a substantial delay in the subjective timing of the C-induced sensation relative to the S-induced sensation. The amount of this estimated change in shift, that is, the delay for C-induced sensation, is close to the actual required

TABLE 3A. SUBJECTIVE TIMING ORDERS OF EXPERIENCES FOR TEMPORALLY-COUPLED STIMULI: (i) PERIPHERAL (S_1 OR FLASH F) AND SOMATOSENSORY CORTEX (C) PAIRINGS, AND (ii) S_1 (OR F)-S_2 PAIRINGS

		C stim.			$S_1(F)$-S_2			*Subject's timing*				
Subject		*cath* / *PR*	*Min. TD (ms)*	*Test TD (ms)*	$S_1(F)$-C	*Interval (ms)*	*No. of trials*	$S_1(F)$ *first*	*T*	S_2/C *first*	*Estim. 'mean shift' (ms)*	*Approx. SD*
J.W. (male, aged 54 y)	A				S_R-S_L	−200	5	0	0	5	−21	10
						−150	12	0	3	9		
						0	12	1	11	0		
						+150	9	9	0	0		
						+200	4	4	0	0		
	B	cath	200	500	S_R-C	−400	6	0	1	5	−241	24
						−300	11	0	8	3		
						0	12	11	1	0		
						+300	5	5	0	0		
						+400	4	4	0	0		
C.J. (male, aged 60 y)	A				S_R-S_L	−200	3	0	0	3	−9	9
						−150	8	0	0	8		
						0	8	1	7	0		
						+150	6	6	0	0		
						+200	4	4	0	0		
	B	cath	~300	700	S_L-C	−200	9	5	4	0	−463	156
						0	7	5	2	0		
						+200	9	9	0	0		
	C	PR	~200	700	S_L-C	−200	6	0	6	0		
						0	4	1	3	0		
						+200	6	1	5	0		
O.K. (male, aged 53 y)	A				S_L-S_R	−200	11	0	1	10		
						0	7	1	5	1		
						+200	10	9	1	0		
	B	cath	~400	500	S_R-C	−500	10	9	1	0		
						−400	7	7	0	0		
						−200	5	5	0	0		
						0	14	11	3	0		
						+200	4	4	0	0		
M.T. (male, aged 42 y)	A				F-S_L	−100	10	0	0	10	15	10
						0	13	1	9	3		
						+100	7	6	1	0		
	B	cath	200–300	400	F-C	−200	11	0	7	4	−80	23
						−150	11	0	7	4		
						0	15	6	8	1		
						+150	10	9	1	0		
						+200	9	8	0	1		

Subject	C stim.			$S_1(F)$-S_2 / $S_1(F)$-C	Interval (ms)	No. of trials	Subject's timing		
	cath / PR	Min. TD (ms)	Test TD (ms)				$S_1(F)$ first	T	S_2/C first
W.M. (male, aged 47 y)	A			F-S_R	−300	15	0	1	14
					−200	33	0	4	29
					0	31	1	26	4
					+200	24	12	10	2
					+300	12	11	1	0
	B PR	200	400	F-C	−400	7	1	1	5
		300	500		−300	11	0	6	5
					−200	17	1	6	10
					0	23	2	17	4
					+200	8	2	6	0
					+300	8	4	4	0
A.E. (female, aged 57 y)	A			F-S_L	−200	25	1	2	22
					−150	23	3	2	18
					−100	13	3	10	0
					0	41	2	38	1
					+100	10	2	7	1
					+150	19	11	6	2
					+200	18	16	1	1
	B PR	~300	700	F-C	−400	22	2	12	8
					−200	16	3	12	1
					0	18	5	13	0

TABLE 3B. COMPARISONS OF TIMING ORDERS, FOR PAIRS OF PERIPHERAL STIMULI VS. PERIPHERAL-CORTICAL PAIRS (C = CATHODAL PULSES)

Subject	Min. TD for C (ms)	Comparison	Estim. 'change in shift' (ms)	Approx. SD	Approx. 95% confidence interval
J.W.	200	A vs. B $(S_R-S_L)-(S_R-C)$	220	25	(169; 271)
C.J.	~300	A vs. B $(S_R-S_L)-(S_L-C)$	454	156	(143; 765)
M.T.	200-300	A vs. B $(F-S_L)-(F-C)$	95	25	(45; 145)

minimum train duration (TD) of 200 ms for C stimulus in J.W.; it is greater than the minimum TD of 300 ms in C.J.; and it is less than the minimum TD of 200 to 300 ms in M.T. (on the latter difference, *see below*). Note also that the 95 per cent confidence intervals all indicate that the change in shift in each case is in the positive range only, that is, in the direction of a delay for timing of C-induced sensation. (Results for O.K. were not treated statistically because the coupling was left–right [S_L–S_R] in block A, but right–right [S_R- and C-induced sensations on the same side] in block B (*see* details in small print section, above). However, the results for subject O.K. in Table 3A are in qualitative agreement with those for J.W., C.J., and M.T.)

These findings are thus in general accord with the prediction from the hypothesis (*see* fig. 3) and also with the results described in Section I of the Results. The substantial relative delay in the subjective timing of the C-induced sensation is of course sharply different from the absence of such a delay for a sensation induced by a comparable LM stimulus train (*see* Section III-B of Results, *above*); for example, compare Table 2B with Table 3B. For subject M.T. the estimated change in shift of 95 ms indicated a relative delay that is less than the 200 to 300 ms minimum TD required by the C stimulus. However, subject M.T. (who was a very alert, introspective observer) reported having a 'hunch', or preconscious type of feeling, that 'something' was building up before the instant at which he himself felt that he was actually aware of a somatic sensation, when elicited with the C stimulus; this would tend to make his reported timings for onset of C earlier than warranted by the criterion for subjective experience. (This interesting phenomenon may in fact be related to an additional hypothesis, that neuronal activities which are too brief for eliciting a conscious experience may mediate unconscious mental functions, *see* Libet, 1965, 1966).

2. *P_1–C couplings using 'polarity reversals' (PR) in pulse train for C.* In 'PR' stimulus trains applied to the unifocal subdural electrode the polarity of each successive pulse was reversed; that is, the polarity alternated between being cathodal and anodal. PR trains should potentially reduce any tendency for the stimulus to produce electrolytic damage to tissues, and so they had been previously employed by us for cerebral stimuli in which a consistent unidirectional polarity of pulses is not essential to the study. It should be noted that PR trains generally required greater peak currents than did cathodal pulse trains, in order to elicit any conscious sensory experience (*see also* Libet *et al.*, 1964; Libet, 1973).

When PR trains were used for the cortical test stimuli in the present study, the reported subjective timings for C relative to the P_1 stimulus did not show the same patterns that were seen for the unidirectional cathodal pulse trains (*see* Table 3A; block C for subject C.J., and block B for W.M. and A.E.). Instead, there tended to be a preponderance of subjective timing reports of 'together', for the P_1- and C-induced sensations, regardless of the coupling intervals between the two stimuli. This is especially convincing in the subject C.J. for whom trials with both cathodal and PR pulses can be directly compared (blocks B vs. C). It would appear that use of PR pulses for C stimuli (a) tends to confuse or blur the subjective experience of timing orders, so that distinctions are less possible; and (b) does not produce the kind of clear evidence of a substantial delay in subjective timing for C that was seen with cathodal pulses. The curious difference between the responses with PR as opposed to cathodal cortical pulse trains may be explainable in terms of the proposed modified hypothesis (*see below*).

Each cathodal pulse would tend initially to excite neuronal elements, probably conducting fibres, that lie in the surface layers of the cortex (Libet *et al.*, 1964; Libet, 1973). The electrophysiological response to each cathodal pulse begins with a large surface negative component; this 'direct cortical response' is different from the primary evoked potential elicited by a peripheral or a lemniscal stimulus pulse (Libet *et al.*, 1967; Libet, 1973). On the other hand, each surface anodal pulse should tend to excite deeper lying nerve fibres (Hern, Landgren, Phillips and Porter, 1962; Phillips, 1969; Libet, 1973), and these might include some of the afferent specific projection fibres from the thalamus which terminate chiefly in layer IV (Colonnier, 1966). This possibility is further promoted by the relatively larger peak currents that were required by PR as opposed to cathodal pulse trains, to elicit the same minimal sensory experience. Excitation of some of these ascending fibres would, according to our hypothesis, provide at least a weak timing signal for retroactive subjective referral. A train of pulses with successively alternating polarities might then provide both the surface cortical and the ascending specific kinds of input alternately, in addition to possible other kinds. In such circumstances, it would hardly be surprising for there to be a subjective confusion about the timing of the sensory experience elicited. Indeed, the nature of these results provides some indirect support for the modified hypothesis. (This analysis suggested the possibility that one or a few surface anodal pulses of sufficient intensity, delivered at a time just before a cathodal pulse train, might provide the signal for shifting the subjective timing of the experience, from the usual position at the end of a minimum TD to a position at the onset of the cathodal C stimulus train. It has, however, been possible to carry out only a few preliminary and inconclusive tests of this kind).

GENERAL DISCUSSION

Overall Evidence for the Present Hypothesis

The results obtained in these experiments provide specific support for our present proposal, that is, for the existence of a subjective temporal referral of a sensory experience by which the subjective timing is retroactively antedated to the time of the primary cortical response (elicited by the lemniscal input). Subjective timing for onset of an LM-induced sensation did in fact appear to occur with no more delay than that for a peripheral (skin)-induced sensation, even though the minimum delay for the stimulus to achieve neuronal adequacy for the LM-induced sensory experience was experimentally set to be at least 200 ms. On the other hand, with cathodal cortical stimuli subjective timings appeared to exhibit relative delays similar to those required to achieve neuronal adequacy. Stimuli to LM (or n.VPL) of course excite specific projection afferents of the lemniscal system, while C-cathodal stimuli (at near liminal intensities) do not. The apparent confusion or blurring of subjective timings found when the C stimulus pulses were 'polarity-reversed' (train of cathodal pulses alternating with anodal ones) is compatible with this interpretation.

An even more startling experimental prediction remains yet to be tested: if the putative timing signal alone were to be delivered at the *onset* of a cortical-cathodal stimulus train, one might expect that the subjective timing of the *cortically*-induced sensation could be shifted or referred, *from* its usual position (at or after the end of the minimum required train duration) backwards *to* the onset of the cortical stimulus train. An 'isolated' timing signal could be generated by a single pulse stimulus in LM, which can elicit a large primary evoked response at the SI cortex with no conscious sensory experience (Libet *et al.*, 1967). However, this experiment would require the placement, in a given patient, of one electrode in LM (or n.VPL) and another over the precise area of the SI cortex that receives the projection of impulses electrically initiated by the LM (or n.VPL) electrode; these conditions are obviously difficult to achieve under the limitations of approaches that are clinically warranted.

Further testing of the proposal can also be sought in the effects of pathological destruction of the specific projection system at cerebral levels. Elimination of the putative signal required for retroactive subjective referral of timing should introduce a substantial delay for the subjective experience even of a peripherally-induced sensation. If the destruction were purely unilateral, one could test for such a delay by comparing the subjective timings for peripheral stimuli applied to homologous sites on the normal and abnormal sides of the body. For this purpose, the same experimental paradigm which was employed in the 'control' series of the present study could be employed; in this, the pattern of reports of relative timing orders for a skin stimulus on the normal side temporally coupled with one on the abnormal side is obtained. Some indications of inadvertent partial tests of this kind may be already apparent in the present study, with subjects who had sustained some partial unilateral sensory losses apparently due to damage in the specific projection system (*see* discussion of 'Negative mean shifts for S_1-S_2 in Table 2A' at the end of Section III-A of Results). A more thorough study of this issue, employing purely peripheral testing in responsive patients who have incurred appropriately located cerebrovascular accidents which produced a severe unilateral 'epicritic' sensory deficit, has been initiated and will be reported separately. For the one suitable patient studied thus far, there did indeed appear to be a delay of 200 to 400 ms in the subjective timing for a peripherally-induced sensation on the abnormal side, relative to one on the normal side.

Alternative Explanations of the Evidence

Some possible alternative explanations of our findings should here be considered. One type of argument would hold that the delay in achieving 'neuronal adequacy' when stimulating LM/n.VPL or somatosensory cortex, as seen in the relatively long minimum train durations required, is simply due to the 'abnormal' route and/or pattern of these inputs. These cerebral stimuli might require a longer time to develop some special neuronal response, for example because of cortical inhibitory as well as excitatory patterns that they might produce. In this view, 'normal' inputs that do not require long minimum train durations (stimuli to skin, peripheral nerve, dorsal columns) would generate neuronal adequacy with no substantial delay; there would thus be no need to introduce the postulate of a subjective referral backwards in time for the experience of the 'normal' inputs, in order to account for their earlier, more immediate subjective timing. This kind of alternative view would seem to be untenable for the following reasons: (a) this view does not account for our experimental observation that the subjective timing for LM stimuli, requiring minimum TDs of 200 ms or more, appeared to show no delay relative to that for skin stimuli. It would still have to be conceded, therefore, that some retroactive subjective referral process can be engaged selectively by the LM stimulus, even if it does deliver an 'abnormal' input; (b) this view would ignore other evidence already strongly indicating that input via a normal peripheral route (skin stimulus) does require a substantial period of cerebral activities before neuronal adequacy for the conscious sensory experience is achieved. The previous evidence included demonstrations (i) of retroactive effects, on the conscious sensory experience for a near threshold skin stimulus, which could be produced by a conditioning cortical stimulus that follows the skin pulse by 200 to 500 ms (Libet *et al.*, 1972; Libet, 1973); and (ii) of the insufficiency of the early components of the cortical evoked responses to a sensory stimulus for eliciting any conscious sensory experience (Libet *et al.*, 1967); (c) other previous findings indicate that the subjective sensory experiences elicited by a stimulus to somatosensory cortex can have 'natural-like' qualities which can resemble those elicited via normal peripheral inputs (Libet, 1973; Libet *et al.*, 1975), although the temporal and spatial features are different (*see* Methods). Also, if the train duration of the cortical stimulus is extended to one longer than the minimum required 'utilization TD' of about 500 ms, the conscious sensory experience is found to continue but with no progressive increase in subjective intensity above that at its onset; this is different from primary motor cortex where any effective stimulus, no matter how weak, elicits a progressively increasing motor response if the stimulus train duration is extended (Libet *et al.*, 1964; Libet, 1966, 1973).

Another alternative explanation accepts our proposal that there is substantial delay in achieving neuronal adequacy with all inputs, peripheral or central; but it would argue that, in those cases where there is apparent antedating of the subjective timings of the sensory experience, the subjective referral backwards in time may be due to an illusory judgement made by the subject when he *reports* the timings. This possibility was raised by Professor Donald M. MacKay in a discussion with the senior author, B.L. On such a basis, the timings of the subjective experience and of the achievement of neuronal adequacy could be actually identical at the time each sensation is elicited, that is, they would both be delayed. However, in those cases in which the neuronal response includes a component due to the fast specific projection, the subject's later report of how he perceives the timing of the sensory experience is assumed to be affected by the previous presence of the primary cortical response. For example, it could be argued that during the recall process, cerebral mechanisms might 'read back' via some memory device to the primary evoked response and now construe the timing of the experience to have occurred earlier than it in fact did occur. Such a possibility cannot be excluded at present, but it requires added assumptions and appears to be less satisfactory than our own hypothesis: (a) for example, if any 'read back' to the primary timing signal does occur, it would seem simpler to assume that this takes place at the time when neuronal adequacy for the experience is first achieved, when the 'memory' of the timing signal would be fresher; such a process would then produce the retroactive subjective referral we have proposed. Whether the later report of antedated timing of the experience is due to an immediate referral (as postulated by us) or to a later 'illusory judgment', the processes involved would be unconscious and 'automatic' in nature and would not be distinguishable by the subject; (b) the alternative explanation based upon later, illusory judgment of timing has a serious deficiency with respect to an important feature of subjective sensory experiences. By retaining delays for the immediate subjective sensory experiences, when they initially and actually occur, this alternative explanation becomes unable to explain the absence of subjective 'jitter' or asynchrony in our experience, when a variety of peripheral sensory stimuli are applied synchronously. At least one factor that should produce differences in the delays for achieving neuronal adequacy with different stimuli, is the strength of the stimulus. (This is based upon the intensity/train-duration relationship for stimuli to LM (or n.VPL), as well as to SI cortex—*see* Libet *et al.*, 1964, 1972; Libet, 1966, 1973; and on the tendency for the subjective timing of a cortically-induced sensation to approximate the end of the minimum train duration, whether the latter is set at 500 or at 200 to 300 ms—*see* Sections I and III-C in Results). One attractive feature of our modified hypothesis is in fact its ability to deal with this difficulty. Subjective referrals, that are retroactive to the early primary evoked response to each sensory input, would make irrelevant any differences among the timings for neuronal adequacy in a group of synchronously initiated inputs; delays for the primary evoked potential are short (10 to 20 ms), and the differences produced by differing intensities of peripheral somatic stimuli are known to be so small as to be negligible for the purpose of subjective timing (*see* Desmedt, 1971).

Roles of Specific Projection System

The specific projection system is already regarded as the provider of localized cerebral signals that function in fine spatial discrimination, including the subjective referral of sensory experiences in space. Our present hypothesis expands the role for this system to include a function in the temporal dimension. The same cortical responses to specific fast projection inputs would also provide timing signals. They would subserve subjective referral in such a way as to help 'correct' the subjective timing (relative to the sensory stimulus), in spite of actual substantial delays in the time to achieve neuronal adequacy for the 'production' of the conscious sensory experience. The temporal functions of the specific projection system need not be restricted to the one postulated here for subjective referral; for example, the fineness of temporal information it provides is probably utilized in behavioural responses to stimuli that involve spatiotemporal sequences (*see*, e.g., Azulay and Schwartz, 1975).

The role at present postulated for the specific projection system would presumably be significant in the subjective awareness of the timing *order* of two inputs (that is, which one appeared first), and not merely of the existence and duration of some time interval between the inputs. In our studies, even young alert normal subjects were not subjectively aware of the order of two somatosensory inputs when the time interval between them was less than 25 to 50 ms; i.e., with these short intervals most of the timing reports tended to be 'together' or 'same time'. This suggests that even if latencies differed by as much as 25 ms or so for primary evoked cortical potentials elicited by two different peripheral stimuli, the two stimuli would be consciously experienced as being either synchronous or having an ambiguous order. Conscious experience of temporal order should be distinguished from forced-choice judgments of order; for example, in the forced choice paradigm the subject is not given the options of reporting that two sensations appear to be either simultaneous or subjectively not definable as to their order. However, even with forced-choice judgments of order the 'difference threshold' for two temporally-coupled stimuli of the same modality has been found to be about 18 ms—*see* Sternberg and Knoll, 1973.

Some Implications for the Mind-brain Relationship

That the time factor in neural coding and decoding of experience could raise fundamental questions for the mind-brain relationship had already been recognized (*see* Lord Brain, 1963). The presently modified hypothesis deals with the problem of a substantial neuronal time delay, apparently required for the 'encoding' of a conscious sensory experience, by introducing the concept of a subjective referral of sensory experience in the temporal dimension. This would introduce an asynchrony or discrepancy between the timing of a subjective experience and the time when the state of 'neuronal adequacy' associated with the experience is achieved. However, the concept of subjective referral in the spatial dimension, and the discrepancy between subjective and neuronal spatial configurations, has long been recognized and accepted; that is, the spatial form of a subjective sensory experience need not be identical with the spatial pattern of the activated cerebral neuronal system that gives rise to this experience. Indeed, both temporal and spatial referrals are here postulated to depend in part upon the ability to generate the same physiological signal, the primary cortical response to the specific projection input. Philosophically, a discrepancy between the 'mental' and the 'physical' in the temporal dimension can be regarded, in a manner analogous to that for the discrepancy in the spatial dimension, as not contradicting the theory of psycho-physical parallelism or correspondence. But a dissociation between the timings of the corresponding 'mental' and 'physical' events would seem to raise serious though not insurmountable difficulties for the more special theory of psychoneural identity (Popper and Eccles, 1977; Libet, 1978).

SUMMARY

Subjective experience of a peripherally-induced sensation is found to appear without the substantial delay found for the experience of a cortically-induced sensation. To explain this finding, in relation to the putative delay of up to about 500 ms for achieving the 'neuronal adequacy' required to elicit the peripherally-induced experience, a modified hypothesis is proposed: for a peripheral sensory input, (a) the primary evoked response of sensory cortex to the specific projection (lemniscal) input is associated with a process that can serve as a 'time-marker'; and (b), after delayed neuronal adequacy is achieved, there is a subjective referral of the sensory experience backwards in time so as to coincide with this initial 'time-marker'.

A crucial prediction of the hypothesis was experimentally tested in human subjects using suitably implanted electrodes, and the results provide specific support for the proposal. In this, the test stimuli to medial lemniscus (LM) and to surface of somatosensory cortex (C) were arranged so that a minimum train duration of 200 ms or more was required to produce any conscious sensory experience in each case. Each such cerebral stimulus could be temporally coupled with a peripheral one (usually skin, S) that required a relatively negligible stimulus duration to produce a sensation. The sensory experiences induced by LM stimuli were found to be subjectively timed as if there were no delay relative to those for S, that is, as if the subjective experience for LM was referred to the *onset* rather than to the end of the required stimulus duration of 200 ms or more. On the other hand, sensory experiences induced by the C stimuli, which did not excite specific projection afferents, appeared to be subjectively timed with a substantial delay relative to those for S, that is, as if the time of the subjective experience coincided roughly with the *end* of the minimum duration required by the C stimuli.

The newly proposed functional role for the specific projection system in temporal referral would be additional to its known role in spatial referral and discrimination.

A temporal discrepancy between corresponding mental and physical events, i.e., between the timing of a subjective sensory experience and the time at which the state of 'neuronal adequacy' for giving rise to this experience is achieved, would introduce a novel experimentally-based feature into the concept of psycho-physiological parallelism in the mind-brain relationship.

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REFERENCES

AZULAY, A. and SCHARTZ, A. S. (1975) The role of the dorsal funiculus of the primate in tactile discrimination. *Experimental Neurology*, **46**, 315–332.

BARTLETT, J. R., DOTY, R. W., LEE, B. B., NEGRÃO, N. and OVERMAN, W. H. (1977) Deleterious effects of prolonged electrical excitation of striate cortex in Macaques. *Brain, Behavior and Evolution*, **14**, 46–66.

BRAIN, LORD. (1963) Some reflections on brain and mind. *Brain*, **86**, 381–402.

COLONNIER, M. L. (1966) The structural design of the neocortex. In: *Brain and Conscious Experience*. Edited by J. C. Eccles. New York: Springer-Verlag, pp. 1–23.

DELGADO, J. M. R. (1955) Evaluation of permanent implantation of electrodes within the brain. *Electroencephalography and Clinical Neurophysiology*, **7**, 637–644.

DEMPSTER, A. P., LAIRD, N. M. and RUBIN, D. B. (1977) Maximum likelihood from incomplete data via the EM algorithm. *Royal Statistical Society Journal, B*, **39**, 1–38.

DESMEDT, J. E. (1971) Somatosensory cerebral evoked potentials in man. In: *Handbook of Electroencephalography and Clinical Neurophysiology*. Edited by A. Rémond. Amsterdam: Elsevier, Vol. 9, pp. 8–82.

—— and ROBERTSON, D. (1977) Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during forced-paced cognitive tasks in man. *Journal of Physiology, London*, **271**, 761–782.

FEINSTEIN, B. F., ALBERTS, W. W. and LEVIN, G. (1969) The use of implanted thermistor electrodes in the therapy of parkinsonism. In: *Proceedings of the Third Symposium on Parkinson's Disease*. Edited by F. J. Gillingham and I. M. L. Donaldson. Edinburgh: Livingstone, pp. 232–237.

—— —— WRIGHT, E. W., JR. and LEVIN, G. (1960) A stereotaxic technique in man allowing multiple spatial and temporal approaches to intracranial targets. *Journal of Neurosurgery*, **17**, 708–720.

GOFF, G. D., MATSUMIYA, Y., ALLISON, T. and GOFF, W. R. (1977) The scalp topography of human somatosensory and auditory evoked potentials. *Electroencephalography and Clinical Neurophysiology*, **42**, 57–76.

HERN, J. E. C., LANDGREN, S., PHILLIPS, C. G. and PORTER, R. (1962) Selective excitation of corticofugal neurons by surface-anodal stimulation of the baboon's motor cortex. *Journal of Physiology, London*, **161**, 73–90.

HIRSCH, J. F., PERTUISET, B., CALVET, J., BUISSON-FEREY, J., FISCHGOLD, H. and SCHERRER, J. (1961) Etude des réponses électrocorticales obtenues chez l'homme par des stimulations somesthésiques et visuelles. *Electroencephalography and Clinical Neurophysiology*, **13**, 411–424.

JASPER, H., LENDE, R. and RASMUSSEN, T. (1960) Evoked potentials from the exposed somatosensory cortex in man. *Journal of Nervous and Mental Diseases*, **130**, 526–537.

LIBET, B. (1965) Cortical activation in conscious and unconscious experience. *Perspectives in Biology and Medicine*, **9**, 77–86.

—— (1966) Brain stimulation and the threshold of conscious experience. In: *Brain and Conscious Experience*. Edited by J. Eccles. New York: Springer-Verlag, pp. 165–181.

—— (1973) Electrical stimulation of cortex in human subjects and conscious sensory aspects. In: *Handbook of Sensory Physiology*. Edited by A. Iggo. Heidelberg: Springer-Verlag, Vol. 2, pp. 743–790.

—— (1978) Neuronal vs. subjective timing, for a conscious sensory experience. In: *Cerebral Correlates of Conscious Experience*. Edited by P. Buser and A. Rougeul-Buser. Amsterdam: Elsevier, pp. 69–82.

—— ALBERTS, W. W., WRIGHT, E. W., JR., DELATTRE, L. D., LEVIN, G. and FEINSTEIN, B. (1964) Production of threshold levels of conscious sensation by electrical stimulation of human somatosensory cortex. *Journal of Neurophysiology*, **27**, 546–578.

—— —— —— and FEINSTEIN, B. (1967) Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science*, **158**, 1597–1600.

—— —— —— —— (1972) Cortical and thalamic activation in conscious sensory experience. In: *Neurophysiology Studied in Man*. Edited by G. G. Somjen. Amsterdam: Excerpta Medica, pp. 157–168.

—— —— —— LEWIS, M. and FEINSTEIN, B. (1975) Cortical representation of evoked potentials relative to conscious sensory responses, and of somatosensory qualities in man. In: *The Somatosensory System*. Edited by H. H. Kornhuber. Stuttgart: Georg Thieme, pp. 291–308.

NASHOLD, B., SOMJEN, G. and FRIEDMAN, H. (1972) Parasthesias and EEG potentials evoked by stimulation of the dorsal funiculi in man. *Experimental Neurology*, **36**, 273–287.

PHILLIPS, C. G. (1969) Motor apparatus of the baboon's hand. *Proceedings of the Royal Society, B*, **173**, 141–174.

POPPER, K. R. and ECCLES, J. C. (1977) *The Self and Its Brain*. Berlin: Springer, pp. 256–259, 362–365.

PUDENZ, R. H., BULLARA, L. A. and TALALLA, A. (1975) Electrical stimulation of the brain. *Surgical Neurology*, **4**, 265–270, 389–400.

STERNBERG, S. and KNOLL, R. L. (1973) The perception of temporal order: fundamental issues and a general model. In: *Attention and Performance*. Edited by S. Kornblum. New York: Academic Press, No. 4, pp. 629–685.

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NOTICES OF RECENT PUBLICATIONS

The Self and its Brain: an Argument for Interactionism. By K. R. Popper and J. C. Eccles. 1977. Pp. 597. Berlin: Springer. Price £9.40; $17.20.

This is a book about—as its two eminent authors put it—'the problem of the relation between our bodies and our minds'. It seems clear that this is not a purely scientific problem; on the contrary, it is one of the most familiar, traditional, and—no doubt—tangled of philosophical problems. On the other hand it might be urged—though by no means all philosophers would agree—that in a sense it is not a purely philosophical problem either, in that perhaps it cannot be fruitfully debated except in the light of, and with the help of, the best available scientific information particularly, of course, about brain structures and processes. If so, the idea of attacking the problem by way of this particular collaborative enterprise looks excellent. Sir Karl Popper is a distinguished philosopher, notable among philosophers for his deep, learned, and longstanding interest in the sciences. Sir John Eccles is a distinguished neurobiologist, notable among scientists for his continuous and eager interest in the wider bearings of scientific work. The book consists of three parts of roughly equal length. The first, by Popper, gives a critical and historical survey of philosophers' theories of the mind-matter relation; it issues, not very tentatively, in the acceptance of 'interactionism'. The second part, by Eccles, surveys with exemplary clarity the present state of our knowledge of the workings of the human brain, and offers also a pretty untentative hypothesis of 'interactionism'. The third part consists of twelve dialogues between the two authors, in which they review the positions on which they agree and some points as to which they differ, and muse together somewhat more at large on the topic as a whole. The text of these dialogues is the record of actual conversations (in 1974) and is presented, we are told, 'more or less in its original form'. It should be said that, though both authors take their stand fairly firmly on 'interactionism', the claims they actually make for their lengthy and absorbing collaboration are notably modest; both, they say, 'think it improbable that the problem will ever be solved', and that 'no more can be expected than to make a little progress here or there'. So: what progress is made?

Well, what form would 'progress' take? It will perhaps help to throw some light on this question if we ask another, extremely basic one, namely: why is there a *problem* about 'the relation between our bodies and our minds'? What *is* the problem? After all, one might think, we all have bodies and minds; and though, no doubt, there is a very great deal about the nature and working of both bodies and minds of which we are ignorant, the very general nature of the relation between them is, one might think, scarcely more than a matter of common, everyday, first-hand experience. Is it not obvious, and a matter of common experience, that our bodies affect our minds, and *vice-versa*? Good physical health, or a moderate intake of alcohol, makes us feel cheerful; a decayed tooth, or a damaged limb, may make us feel pain; a damaged or defective eye affects the way we see, and a firm knock on the head may make us lose consciousness altogether. Conversely, the wish to consult a certain book, and the knowledge that it is on a shelf in my study, results in my limbs so moving that I go there to get it; the intention to go to London results, eventually, in movement to that location of both my body and my car; the thought of a joke, or of a new philosophical argument, gives rise to the physical movements of speech or writing. In short, if one had to put it into a word, in the course of our everyday lives our minds and our bodies *interact*. What could be more familiar, more immediately obvious, than that? And if so, why do our two distinguished authors need to be so modest? If 'interactionism' is what they are arguing for, is it not luminously obvious that they are right? Where is the problem?

The problem is, of course, that, although 'interactionism', when expressed in the form of such everyday examples as those mentioned, looks quite obviously true, yet, when one comes to consider rather more analytically what one is actually saying when one says that minds and bodies interact, it may come to seem that one is saying something completely *unbelievable*. (Unbelievable, and also undeniable—that is what makes it a classical philosophical problem.) What, at least on the face of it, interactionism appears in general to assert could be put like this. In the history of a human being (and possibly of some other animals too) there occur both physical states and physical happenings, and also mental states and mental happenings; some physical states and happenings cause (at least in part) mental states and happenings; and some mental states and happenings cause (at least in part) physical states and happenings. But is it really possible to swallow that? Can one really accept the idea of a physical state or happening which has, as an effect, something that is not a physical state or happening at all? How could that be? Or—perhaps far worse—can one accept the idea of a physical state or happening which is not caused by *any* antecedent physical state or happening? Could that possibly be? For if so, we should have the extraordinary phenomenon of a physical system—a human body, and in particular a nervous system and brain—composed of perfectly familiar, unsurprising though no doubt very complex chemical compounds, the successive states of which would in principle *not* be causally explicable in terms of antecedent physical states and inputs, in accordance with known and otherwise familiar principles of chemistry and physics. Human bodies, and in particular nervous systems and brains, though they appear to be ordinary enough specimens of physical objects, would have to be supposed to be completely unique exceptions to all known physical laws, their behaviour simply not describable, even in principle, in the same terms as that of the rest of the (after all rather extensive) physical universe. Perhaps we do not know that they are not unique in this way; but certainly we do not know that they are; and can it, in the meantime, really be sensible to believe it?

What so many philosophers and scientists, at any rate since the seventeenth century, have fundamentally found it impossible to believe is that, in this single, unique respect, the physical world is not, as one might put it, 'closed'. It has seemed to them almost axiomatic that physical changes have, and are in principle explicable in terms of, physical antecedents, and have physical effects which they in turn explain. The idea that there are any physical changes not determined by, and even in principle not predictable on the basis of, antecedent physical states and happenings has seemed to them simply incredible, a sort of superstition, and furthermore, a superstition suspiciously flattering to human self-importance. Thus, many attempts have classically been made to describe 'the relation between our minds and our bodies' in ways such that this seeming superstition need not be accepted. It has been suggested that, while there are both physical and mental happenings, these constitute merely *parallel*, not intersecting, series, neither series supposed to be 'open' to mysterious intervention by members of the other. It has been suggested that mental states are merely *epiphenomenal* to—a caused but causally inefficacious froth, so to speak, upon the surface of—a series of physical happenings completely explicable in its own terms alone. More recently, it has been boldly contended that mental happenings can indeed both cause and be caused by physical happenings, but that they *actually are* physical happenings themselves, that mental states and some physical states are, in a sense not at all easy to explain, identical. Popper and Eccles will have none of this. They insist that mental states and happenings are genuinely, irreducibly distinct from physical states and happenings; that mental happenings not only have physical causes, but can have physical effects; and hence that, as the term 'interactionism' of course implies, the world of physical happenings really must be supposed to be 'open' to non-physical intervention. Their 'problem', essentially, is then to make this believable.

Their attempts to achieve this, certainly of the greatest interest, follow partially the same course, but in one important respect appear to diverge. Both, very properly, insist upon a simple and traditional challenge. Confronted with the question 'Can you seriously believe that the physical world is "open" to non-physical intervention?', both ask in reply 'Can you seriously believe that it is not?'. That is: can it really be believed that all the works and doings of men—the composition of a symphony, for example, the working out of a proof in mathematics, or perhaps even the simplest of deliberate, intentional actions—could in principle be *completely* accounted for in terms of movements of bits of matter in accordance with merely physical laws? This is doubtless important, but in a sense of limited interest, since it does not really do much more than restate the problem—that 'interactionism', while on the one hand it seems impossible to believe, on the other hand seems also impossible to deny. More effectively, both insist upon the less familiar point that, if even the most highly developed, fully self-conscious human mind were supposed to *make no difference* to the actual course of physical happenings in the world, it would seem completely mysterious why so elaborate a phenomenon should ever have evolved. Must it not be supposed to give—as of course it appears emphatically to do—some evolutionary *advantage*, and what is that but to say that it makes a certain difference in what actually happens?

Our two authors somewhat diverge, however, in ways perhaps natural to the professional preoccupations of each. Popper, as a philosopher of science, makes a certain effort (*see*, particularly, pp. 539–43) directly to undermine the authority, to call in question the quasi-axiomatic status, of the supposition that the physical world is 'closed'. We have, he points out, long abandoned the idea that all physical processes are fundamentally merely mechanical (the 'billiard-ball' theory of the seventeenth and eighteenth centuries). We have even abandoned the idea that physics must be, or even could be, a rigidly deterministic system. So, if it is now suggested that some physical happenings are not explicable in terms of purely physical antecedents, are we not now really in a position to say: why not? Is that any longer so difficult to believe?

Eccles, on the other hand, is clearly very strongly attracted by a line of argument which looks less promising, and may even be thought to be in principle misconceived. Fortified by his massive knowledge of the workings of the nervous system and brain, he clearly thinks it possible at least in principle to determine *where* the intervention of mental happenings takes place (*viz.*, mostly in the left hemisphere); and he clearly attaches great importance, also, to establishing that such intervention is *only a little one.* But this looks unpromising, for two reasons. First, what his opponent finds difficult to swallow, surely, is the idea that non-physical intervention in physical processes can occur *at all*; and such an opponent is not going to be placated by being assured that it occurs just a little bit. (The French lady, being told of an executed man who had achieved the remarkable feat of walking from Versailles to Paris with his head under his arm, replied 'Ah, monsieur, dans une telle situation, c'est le premier pas qui coûte!') If we are asked to believe that the mind can directly, non-physically bring about physical changes, we are not going to find this easier to swallow on being told that the changes are very little ones, or that they occur in this region of the brain rather than that. That happenings in the left hemisphere are particularly linked with consciousness may of course be scientifically true and important, but seems not, as it were, metaphysically pertinent. The second point, perhaps a more serious one, is that this line of argument seems to lead Eccles inexorably into saying things which, at least on the face of it, are scarcely intelligible at all. He is purporting to tell us what 'the mind' does, or at any rate what he calls the fully human, 'self-conscious' mind; and both authors prefatorily insist that, in their text, 'the word "mind" is used as in ordinary language'. But when it comes to, so to speak, fitting the mind into the workings of the brain in the sort of way that Eccles is in search of, his text seems repeatedly to fall into a kind of nonsense, or at best of profound obscurity. Does it really make ordinary sense to say that the mind—the *self-conscious* mind—is constantly doing things (even tiny things) in a certain region of the brain, which certainly no possessor of such a mind ever is or could be conscious of doing? The 'SC mind' is even said (for example, p. 362) to do these things *in order to produce* consciousness; in what way, then, can it *be* (as terms are used in 'ordinary language') a self-conscious mind? Apparently, also, the 'SC mind' (for example, p. 482) can *move about*—for instance, across the corpus callosum; but does it make any 'ordinary language' sense to describe a person's mind as moving about inside his brain? Again, Eccles has (for example, p. 371) the 'SC mind' incessantly active even during dreamless sleep, even when the person is, as we say, completely unconscious; but can (in 'ordinary language') a self-conscious mind be hard at work when its possessor is actually not conscious at all? It is indeed pretty clear, in all these and other instances, that there is something of substance which Eccles wishes to say; but it may well be thought that he is far from having found a perspicuous way of saying it, and that, for him, it cannot be enough simply to say that he always means by 'the mind' just what we all ordinarily mean by it. Popper (who has a notably low opinion of most other contemporary philosophers) always, as here, characteristically insists that 'verbal' issues are of no interest or importance. But we ordinarily talk about minds in one sort of way, about brains (and other physical objects) in a very different sort of way. The attempt to discuss—as this book most absorbingly does—the relation of minds to brains involves (of course among other things) the most intricate exercise of trying to link these widely different ways of speaking, and cannot possibly be served by mere carelessness at this crucial point. One feels that Popper's prejudices may have prevented him here from helping Eccles in ways that a lesser philosopher might have done.

G. J. WARNOCK

Neuro-ophthalmology. By Joel S. Glaser, with contributions by R. B. Daroff, L. F. Dell'Osso and B. T. Troost. 1978. Pp. 364. Hagerstown, Maryland: Harper and Row. Price $35.00.

Neuro-ophthalmology has long been a particularly attractive field of study for neuroscientists. There is something for everyone: retinal and cortical aspects of visual perception, the control of eye movement and the maintenance of binocular synchrony during pursuit and saccadic movement continue to occupy workers in basic research. For the clinician, whether ophthalmologist, neurologist or neurosurgeon, there is endless fascination in the sheer range of signs produced by lesions in the visual system and, increasingly, much of practical value in diagnosis and management of disorders involving the afferent and efferent connections. It can be no accident that two of the pioneers in the field, Young and Helmholtz, based their distinguished contributions to physics on their neuro-ophthalmic observations. Helmholtz' own *Handbuch der Physiologischen Optik* is, happily, still available in English.

Dr. Glaser and his colleagues, Drs. Daroff, Dell'Osso and Troost have produced a treatise of neuro-ophthalmology which perfectly complements the larger and well-known three-volume work of Walshe and Hoyt. The emphasis throughout is on clinical phenomena, and the book is beautifully illustrated with photographs, line diagrams and electrophysiological recordings. While no attempt has been made to assume the role of encyclopædia the enquiring reader will find few clinical phenomena not mentioned. References to the literature are appropriate and up to date throughout the book. Nearly a third of the book is occupied by a discussion of disorders of ocular movement and this, reflecting the unique experience of its authors, is the real strength of the book. Dell'Osso and Daroff, in a series of exceptionally clear block diagrams have summarized current concepts of the organization and control of fast and slow eye movements, including an account of the interaction of vergence and version systems. This enables their account of supranuclear disorders, nystagmus and infranuclear disorders to be illustrated by reference to these basic ideas, and so order is brought into what might otherwise be a chaotic list of different phenomena.

The student must remember that this volume forms part of Duane's *Clinical Ophthalmology*, so that some important traps for the unwary neurologist, for example, simple glaucoma as a cause of primary optic atrophy, receive only a very brief mention. Perhaps this effect of the specialization inherent in the plan of the book should have been made clearer in the preface.

M. SWASH

Handbook of Physiology. Section 1. **The Nervous System.** Volume 1. Cellular Biology of Neurons. Parts 1 and 2. Edited by Eric R. Kandel. 1977. Pp. 1182. Baltimore: The American Physiological Society and Williams and Wilkins Company. Price $135.

It is of course a byword that a 'Handbook' is anything but a book that can be easily held in the hand. These two massive and very expensive tomes printed on large size glossy paper can only be read at a desk, and fitting with that is the content. They are in no way easy reading and not always a good introduction even for third year Honours students, to the wide range of topics covered, for by their very obsessionalism which makes almost all chapters marvellous sources of reference to the literature, most of the authors manage to create the ideal environment in which sight of the wood is rapidly lost by the dense thickets of trees. This also, in spite of what is said in the preface, does remove the excitement of much of current neurobiological research. The topics which are included are morphology of neurons and neuroglia (one chapter), excitation and conduction of nerve impulses (5 chapters), junctional transmission (12 chapters including one on axoplasmic transport), cellular interactions (4 chapters on tissue culture, glial cells, trophic interactions and specification of neuronal interconnections), systems of neurons (spinal neurons, olfactory bulb, and supraspinal neurons), and neurons and invertebrate behaviour (3 chapters). The index is adequate but not as good as one would wish in a book which is primarily a source of reference. An apparent delay in publication also means that the references end in 1974 and already in certain topics the chapters are clearly out of date. This tendency to date is an inevitable consequence of the pace of current research.

It is fairly certain that these two books will not be bought by individuals, at least not without protracted negotiations with their bank managers, but libraries should probably dig deep into their funds and get them, for when all is said and done they contain a very useful and workmanlike collection of articles. One does wonder, however, how many more volumes will be needed (and at what expense) to complete this microscopic examination of the CNS.

M. C. BROWN

Antiepileptic Drugs: Quantitative Analysis and Interpretation. Edited by C. E. Pippinger, J. Kiffin Penry and Henn Kutt. 1978. Pp. 400. New York: Raven Press. Price $38.35.

This book was written in response to demand from participants at the 1976 symposium at Kansas City on the 'Reliable Quantitation of Antiepileptic Drugs' for an authoritative account of current knowledge on the therapeutic monitoring of antiepileptic drugs.

There are twenty-eight short chapters all written by acknowledged authorities almost exclusively from the USA. They fall into two main sections plus an appendix.

The first section deals with analytical techniques and quality control and will be of most use to those giving a routine anticonvulsant drug service. Many topics which have exercised laboratory biochemists over the past ten years are dealt with clearly and concisely including gas liquid chromatography (GLC), instrumentation, internal standards, techniques of derivation by methylation and the relative advantages of GLC and homogenous immunoassay (EMIT). Analysis of the six commonly used anticonvulsants is discussed individually and precise technical details are given in the Appendix; this will be useful for laboratories in the process of setting up a service for the first time.

Space is also devoted to more specialized techniques including electron capture—GLC, nitrogen detectors, high pressure liquid chromatography, radioimmunoassay, and mass spectrometry, and these are discussed in relation to the assay of a wider range of drugs including the benzodiazepines.

The remaining nine chapters deal with the clinical applications of antiepileptic drug concentrations in plasma, covering both the pharmacokinetic principles involved and the clinical usefulness of monitoring individual drugs. A final chapter deals with the special problems encountered in pædiatrics.

Whilst some guidance is given concerning accepted therapeutic ranges in plasma in man, detailed biochemical discussions are not to be found in this book and it is a pity that more attention has not been given to the important question of drug interactions both between anticonvulsants themselves and other therapeutic agents. Clinical pharmacologists and clinicians interested in reading about the subject in depth would find little of substance in this section, which is primarily intended as an introduction to the subject. To this end, however, it is well written and gives an authoritative and balanced account of knowledge at the time of writing.

The book is well produced, the figures and legends clear and the bibliography adequate up to 1976.

P. T. LASCELLES

A Barefoot Doctor's Manual. Revised and enlarged edition, 1978. Prepared by The Revolutionary Health Committee of Hunan Province. Pp. 372. London: Routledge and Kegan Paul. Price £5.95, paperback.

This book will be of great interest to anybody who has wondered what kind of training Chinese 'barefoot doctors' (medical auxiliaries) are getting. In view of the obvious great strides public health in China has made during the last decades, and the decisive role attributed to the barefoot doctors in this progress, a manual written for the medical auxiliaries of Hunan Province and translated into English brings most welcome information. Its first edition was published in 1974 by the Fogarty International Center, Bethesda, and the second, improved and enlarged edition has appeared last year in the USA and is now published in this country.

A simple anatomical introduction which does not burden the student with names forms the beginning of the manual, followed by short chapters on hygiene, diagnostic and therapeutic techniques and birth control. The next two chapters are the backbone of the book: the first deals with the main diseases, each disease being first described, and then classified, if appropriate, into its Chinese subdivisions. This is followed by a paragraph on prevention and by the various therapeutic treatments: a few lines on 'new acupuncture therapy', a detailed description of treatment by herbs, and, usually, a short passage on the use of Western drugs. Some diseases can also be treated with massage, cupping or the rather heroic 'moxibustion'.

It is interesting to find (p. 13) that the physiological role of the spleen in traditional Chinese medicine is not that which it is given in the West. The Western reader will also find it strange that influenza and malaria or infestation with ascaris might be treated with acupuncture. Other parts of the manual, such as the first aid instructions or the Tables for differential diagnoses could have been composed in the West. It is reassuring to read that the initial treatment is usually meant to be symptomatic, but should be followed by 'treatment of etiological factors', and, if treatment is not successful, the patient should be sent to hospital. Another important comment deals with leukæmia and states that this should be treated by 'a combination of Chinese and Western medicine' while the search for efficient remedies is continued.

The last chapter describes 522 medicinal 'herbs', of which over two-thirds are illustrated with drawings. The Chinese name is followed by the Latin name, and the herb's appearance, action, indication and the preparation of the remedy are described. An Appendix surveys recent experimental work on herbal medicines and their pharmacology. There are good indexes at the end of the book.

The book is well produced although there are still some errors in translation, such as to suggest 10 per cent formaldehyde instead of paraldehyde in the treatment of tetanus.

It does not answer the question how many barefoot doctors prefer herbs or how many use Western drugs in their prophylactic and therapeutic measures. Meanwhile, as indicated in Appendix A (pharmacological and clinical data on herbal medicines) Chinese pharmacologists use modern scientific methods to assess the value of herbal treatment, and there is no doubt that this will have an important effect on future prescriptions and guide lines.

M. VOGT

Brain Energy Metabolism. By B. K. Siesjö. 1978. Pp. 607. Chichester: John Wiley. Price £17.50.

Siesjö has written an excellent account of brain energy metabolism which not surprisingly lays emphasis on the coupling of function, metabolism and blood flow in the brain. The book, well organized into fifteen chapters, is easy to read. The subject matter of each chapter leads logically into the next and there are no unwieldy biochemical formulæ. Fundamental topics, such as thermodynamic principles, intermediary metabolism and glucose transport, are summarized first. In the second part topics such as anæsthesia, control of mental activity, epileptic seizure, hypoglycæmia, hypoxia and ischæmia are fully discussed. This book is highly recommended to neurologists and brain scientists in research and training.

D. M. BOWEN

Radiology of the Skull and Brain. Volume 3. **Anatomy and Pathology.** Edited by T. H. Newton and D. G. Potts. 1977. Pp. 3333. London: Henry Kimpton; Saint Louis: Mosby. Price £37.45.

The book begins with a long, extensively and beautifully illustrated chapter showing the comparative anatomy of the ventricular system from elasmobranch to man. The photographs of whole brains and radiographs of barium-filled ventricular systems are supported by a lucid, learned and well-documented text. The 127 pages of this chapter would be useful reading for all those studying any of the neurosciences.

There follow chapters on CSF circulation, the anatomy of the normal human brain, and pathology of congenital abnormalities of the brain that hang together well without repetition.

The rest of the book consists of five chapters devoted to pathology; that on infections and allergic and demyelinating diseases of the nervous system is written with CAT scanning very much in mind, diagrammatic slices being used to demonstrate the distribution of disease. These pathology chapters fulfil their intention of a review and reference for neuroradiologists for whom there is no similar text, but it is a pity that the vascular system is treated only from the morphological point of view. So much of the understanding of pathology really depends upon a knowledge of physiological and functional disturbance.

The volume is a very worthwhile addition to Newton and Potts, the major text book for neuroradiologists.

GEORGE DU BOULAY

The Biochemical Basis of Neuropharmacology. Third Edition. By J. R. Cooper, F. E. Bloom, and R. H. Roth. 1978. Pp. 327. New York: Oxford University Press. Price £3.95.

Although this small book is on neuropharmacology reference to drugs is strictly limited. The reader will find neither a systematic account of drug metabolism nor tabulated details of their action in the nervous system. Thus there is only a restrained yet critical account of the dopamine hypothesis of schizophrenia and relatively little on the mode of action of neuroleptics on adenylcyclase. This is because the authors contend that there is still a large gap between descriptive knowledge of neurotropic agents and the understanding of molecular mechanisms. Apart from local anæsthetics, neuropharmacological agents seem to be involved with events at the synapse. The authors have therefore understandably concentrated on describing current knowledge of neurotransmitter biology. There are excellent chapters on acetylcholine, catecholamines, serotonin, amino acids, neuroactive peptides and on cyclic nucleotides, prostaglandins and histamine. Each chapter contains a section on the localization, physiology and metabolism as well as the pharmacology of the transmitter. The popularity of this small book is fully deserved for there are few examples of such clear and readable accounts of the biochemistry of neurotransmitters. It can be particularly recommended to clinicians wishing to bring themselves up to date with the scientific basis of neuropharmacology.

A. N. DAVISON

Handbook of Clinical Neurology. Vol. 33. **Infections of the Nervous System,** Part 1. 1978. Pp. 560. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: Elsevier/North-Holland. Price Dfl.191.25.

This volume covers bacterial infections of the nervous system. There are comprehensive chapters on brain abscess and infections of the cranial dura and dural sinuses by Garfield and Bernard Smith respectively. Volume 33 contains more contemporary references than its immediate predecessor. The clinical and pathological parts are generally well written and genuinely comprehensive. While some sections on treatment are less helpful than the other parts of the book, the reviewer was sharply reminded of the international nature of the Handbook by Tandon's recommendation of ethambutol or rifampicin 'for those who can afford it', in the treatment of tuberculous meningitis. This is a further useful member of the series.

R. A. HENSON

Neurology. Proceedings of the 11th World Congress of Neurology. Edited by W. A. den Hartog Jager, G. W. Bruyn and A. P. J. Heijstee, 1978. International Congress Series No. 434. Pp. 437. Amsterdam: Excerpta Medica. Dfl. 155.00.

Criticism of large international congresses is a currently fashionable pursuit. One target has been the opening ceremony with its mandatory welcomes and eulogies, but neurological scientists present at Amsterdam will testify to the admirable content and brevity of the several addresses delivered on that occasion. *Neurology* contains these addresses and the invited papers from a truly international team on the main topics of the congress. The topics were neuroimmunology, neuromuscular disorders, disturbances of consciousness and cognition and geographic factors in neurology. The permanent record of this successful meeting will be welcomed by those who were present, and it is commended to those who were not. Unfortunately, the price of the well produced volume is high.

R. A. HENSON

Essays in Neurochemistry and Neuropharmacology, Volume 3. Edited by M. B. H. Youdim, D. F. Sharman, W. Lovenberg and J. R. Lagnado. 1978. Pp. 228. Chichester and New York: Wiley. Price £10.50.

This is the third volume of 'Essays', and it should be very useful to many readers. The first article, from Aghajanian's pen, summarizes most clearly similarities and differences between feedback regulation in the three main monoaminergic systems of the brain. The author's extensive experience in the field makes the essay particularly fascinating. The next three chapters deal with the actions of the nerve growth factor, with the suitability of platelets as a model of central aminergic neurons, and with the question whether availability of tryptophan controls not just brain content of 5-hydroxytryptamine but also the activity of tryptaminergic neurons. A long article (by K. G. Lloyd) summarizes the extensive literature on the interaction between neurons containing dopamine and those using other transmitters, a subject of particular importance in the physiology and pathology of the striatum. The book concludes with a discussion of the principles involved and the fallacies to be avoided in trying to establish a biochemical basis for memory.

M. VOGT

Brain

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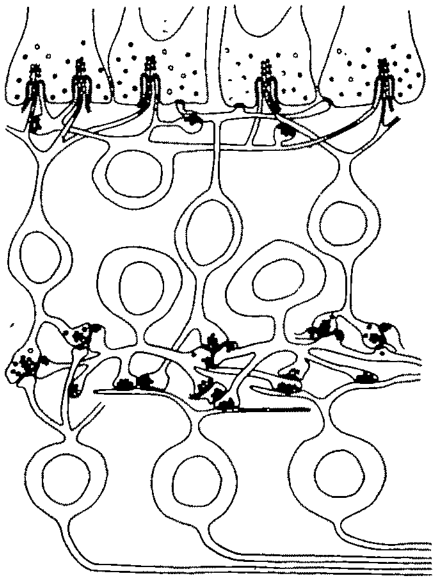

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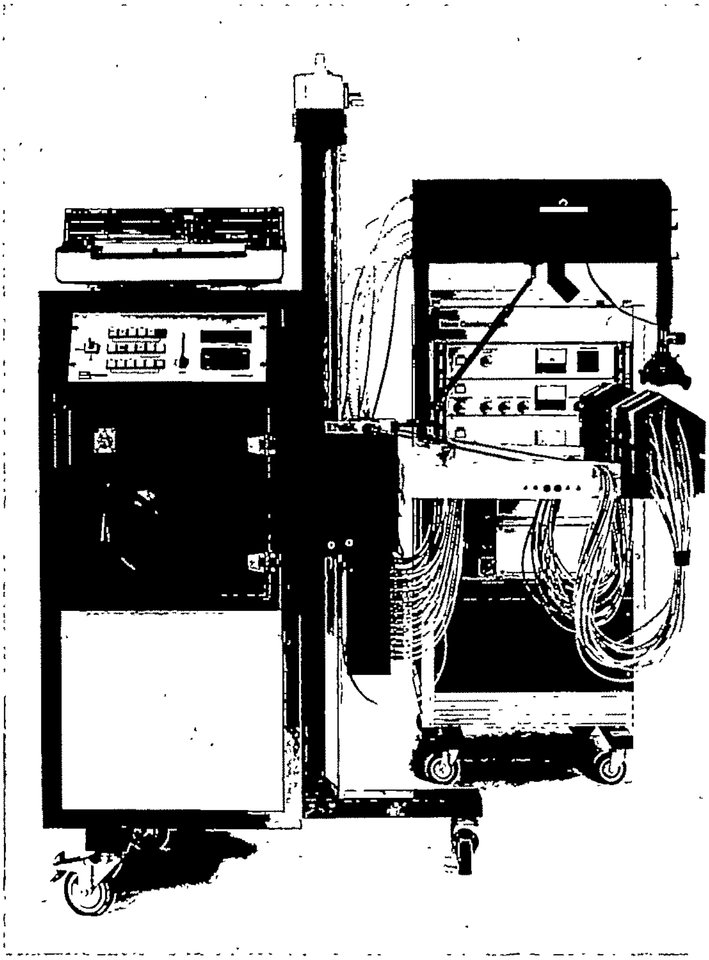

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THE IMPACT ON NEUROLOGY OF 40 YEARS' ADVANCES IN PHARMACOLOGY[1]

by MARTHE VOGT

(*From the Agricultural Research Council, Institute of Animal Physiology, Babraham, Cambridge CB2 4AT*)

IT is now half a century ago that I became a doctor and a pharmacologist, and this has made me a witness of the most spectacular advances in biochemistry, pharmacology, neurobiology and therapeutics, which still proceed at what seems an ever-increasing pace. It is to some of these advances and their impact on neurology that I wish to devote this article.

Sulphonamides

Shortly before the outbreak of the last war, Domagk (1935) announced that a derivative of sulphanilamide would cure streptococcal infections in mice. This went against the dogma, believed in at the time, that most bacterial infections, in contrast to protozoal disease, could not possibly be cured by drugs without at the same time killing the host. However, by making use of differences between the metabolism of the host and that of the bacterium, such a feat can be achieved. Thus the mode of action of sulphonamides was soon discovered to be competition of the drug with uptake by the micro-organisms of p-aminobenzoic acid, an essential building block used in their synthesis of folic acid.

The sulphonamides concern us here because they were the first drugs effective in meningitis. Now they are rarely used, since penicillin soon became the drug of choice.

The therapy of another serious plague of mankind, leprosy, made progress at the time of the discovery of the sulphonamides: Buttle, Stephenson, Smith, Dewing and Foster (1937) showed that the related drugs called sulphones were effective in streptococcal infections; they are more toxic than the sulphonamides, but attack acid-fast bacilli, and by 1941 the first successful clinical trials in leprosy were under way.

Penicillin

I can be brief about the work leading to the manufacture and first therapeutic uses of penicillin and of the host of antibiotics which followed it, since it is such a well-known story. The discovery of a substance formed by moulds which arrested bacterial growth was made in 1928 by Fleming, who did not find a way of isolating a stable compound; but at the beginning of the Second World War Florey, in the Oxford Pathology Department, joined by a number of co-workers, started a systematic search for a method of isolating and purifying penicillin in order to obtain a product which would be non-toxic and prevent or cure bacterial infections. With Chain, the chemical isolation was achieved during the early part of the War, but manufacture of sufficient quantities by incubating the penicillin mould in bulk was achieved in the USA; penicillin revolutionized the treatment of war wounds, including brain injuries. In addition, it is highly effective in meningococcal meningitis. Though it does not easily pass the blood-brain barrier, it penetrates to some extent the inflamed meninges, so that intrathecal therapy is not always required. Among all the antibiotics discovered and employed since the isolation of penicillin, none can compete with it in its complete lack of toxicity to the host. This picture is only marred by the possibility of the development of hypersensitivity reactions and, of course, the curse of all antibacterial and anti-protozoal therapy, the development of resistance of the pathogen.

---

[1] Based on a talk given on April 5, 1978 at the Centenary of Brain.

The availability of a chemotherapy against the majority of bacterial infectious diseases has had two other consequences which are of interest to the neurologist: (1) the tremendous increase in life expectancy has necessitated the treatment of many more old people than in the past, so that the whole subject of geriatrics has grown considerably, and the ageing brain has, alas, become of paramount social and medical importance; (2) a number of viral diseases of the brain and cord, previously either unrecognized or overshadowed by the well-known bacterial infections, has become a very important field for research and therapeutic effort.

Other Discoveries

Before dealing with the developments which have revolutionized life on the psychiatric ward, a few isolated discoveries should be mentioned which were made during and after the last war and which have greatly widened therapeutic possibilities. The shock therapy of psychoses with pentetrazol (leptazol) was initiated in 1939 by von Meduna and co-workers, and, a year later, Bennett suggested that it should be combined with d-tubocurarine in order to reduce the danger of fractures or dislocation of bones. Since 1942, when Griffith and Johnson demonstrated that d-tubocurarine could also be a safe and effective muscular relaxant in anæsthesia, its use during operations has spread widely; in addition to the natural compound, there are now many synthetic analogues available for the same purpose. During the 1950s, a non-flammable, non-explosive volatile anæsthetic halothane, which is less toxic than chloroform, made its appearance. Animal experiments carried out by Raventos showed its efficacy, and clinical trials by Johnstone confirmed its usefulness in man. Although its administration requires special equipment, it has largely replaced other volatile anæsthetics. In 1968, an unexpected finding by Millichap, that the amphetamine-like stimulant methylphenidate is particularly useful in the treatment of hyperkinetic children, supplied the neurologist with yet another helpful tool.

However, by far the most dramatic therapeutic progress during the last twenty-five years has been the discovery that drugs can improve psychoses. This has revolutionized the outlook for mental patients and allowed the psychiatrist to use powerful drugs instead of maiming surgical interventions or a purely sedative therapy. Even if not curing the patient, the treatment may improve his condition to the extent that he can lead a tolerable life outside the hospital ward and not be an excessive burden to his family. Attempts at explaining the mode of action of the drugs which benefit psychotic patients have led to theories about the underlying causes of mental disease. Since all effective drugs interact in various ways with catecholamines or indolamines, anomalies in the neurons containing these monoamines have been suggested as causes of the psychotic condition. This topic will be discussed later.

Schizophrenia

In 1952, Laborit and co-workers used a drug, synthesized as an antihistamine, as part of what he called 'lytic cocktail', to lower body temperature during serious operations. It was soon discovered that this drug, then called 4560 RP, and now chlorpromazine, had a multitude of effects; Delay, Deniker and Harl, in 1952, used it in a mixed group of psychoses and reported this treatment to be better than any previously attempted drug therapy inasmuch as it 'reduced both agitation and confusion'. I think chlorpromazine is unique in having remained, twenty-five years later, in use and of very great value in the treatment of schizophrenia, mania and other psychotic states. A very large number of related compounds have swamped the market but have rarely proved of appreciably greater benefit.

Chlorpromazine has, of course, its side-effects. The best known of these are Parkinsonian signs, which may be followed by tardive dyskinesia. The Parkinsonism is thought to be caused by a block of dopamine receptors in the striatum. The fact that chlorpromazine and related antipsychotic drugs interfere with dopaminergic neurons has led to a theory that schizophrenia is due to excess dopaminergic activity, a theory which is far from proven but has stimulated a great increase in the study of the fate of dopamine, and the actions of dopaminergic neurons, in the brain. For such a theory to become acceptable, it was essential to discover sites of dopaminergic neurons outside the well-known nigrostriatal pathway, since the functional role of this pathway seems to be essentially sensory-motor. This condition became fulfilled by the discovery of what are now known as the mesolimbic and mesocortical dopaminergic pathways for which roles in emotional and mental activities are not *a priori* unlikely (*see* Nonstriatal Dopaminergic Neurons. Edited by E. Costa and G. L. Gessa. *Advances in Biochemical Psychopharmacology*, **16**, 1977).

Yet, there are a number of difficulties about this theory, which cannot be discussed adequately in the frame of this historical review, but it should be stressed that clinical improvement by suppression of dopaminergic activity does not necessarily mean that the disease is primarily one of the dopaminergic neuron. This would be like saying that Parkinsonism is a disease of the cholinergic system because it is improved by atropine. Furthermore, the suspicion once held that the best antipsychotic compounds within the phenothiazines are those which are most likely to cause Parkinsonian side-effects has not been confirmed. For example, after treatment with two related phenothiazines, chlorpromazine and thioridazine (*see* fig. 1), there is a high incidence of Parkinsonism after the first and a very low one after the second compound. Yet thioridazine is found by many clinicians to be equalling chlorpromazine in antischizophrenic activity. Thus there is dissociation between the effects of these drugs on the striatum and those on the psychotic process.

The latest hopes to find a biochemical fault in schizophrenia have arisen from observations on endorphins which will be discussed later on.

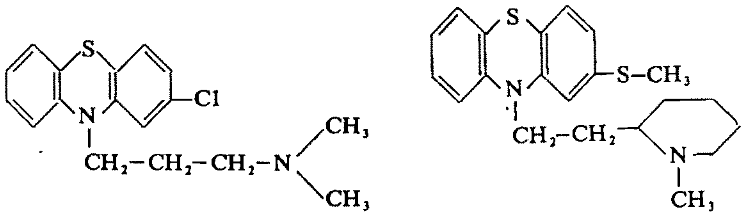

FIG. 1. Formula of chlorpromazine on the left, of thioridazine on the right.

Depression

The first success (in 1957) in the treatment of depression was achieved with iproniazid. It followed the observation that tuberculous patients given this drug became excited and were in high spirits. Since iproniazid is an inhibitor of monoamine oxidase (MAO) and increases brain amines, a lack in catecholamines and perhaps in 5-hydroxytryptamine, it was argued, may underlie the disease. This was supported by findings of low concentrations of metabolites of noradrenaline and 5-hydroxytryptamine in the CSF of patients. Iproniazid was followed by other MAO inhibitors which were found successful too, but there was no correlation between potency as inhibitors of the enzyme and as antidepressants. Next (1958) the tricyclic drugs, such as imipramine, were discovered to be effective in depression, and their property to inhibit reuptake of amines was thought to be responsible for their usefulness. However, the slow onset of the therapeutic effect was not explained by this hypothesis. A recent theory (Sulser, Vetulani and Mobley, 1978) suggests that the fault lies not in a lack of amines but postsynaptically in the receptors. In the limbic forebrain of the rat, noradrenaline, released at the synapse, by combining with its receptors activates a cyclic AMP generating system. Chronic, but not acute, treatment with cyclic antidepressants, MAO inhibitors or electroconvulsive shock was shown to decrease the reactivity to noradrenaline of this cyclic AMP generating system. The theory suggests that this system is present in the human brain and that the noradrenaline receptors are hypersensitive in depression. Such an explanation of the disease would consider the low levels of monoamine metabolites found in the CSF of depressives to be a consequence of the enhanced receptor sensitivity, and not the cause of the depression. However, these views have not gone unchallenged. Green (1978), for example, concludes from his experiments that electroconvulsive therapy acts in depression by *in*creasing, not by *de*creasing, receptor sensitivity! Irrespective of the outcome of this controversy, it seems to me that the new stress on the state of the receptors rather than on the amount of transmitter released is a promising step forward.

Lithium

In 1954, Schou, Juel-Nielsen, Strömgren and Voldby carried out an extensive trial of the administration of lithium salts to manic patients. In the course of the years, this treatment has gained acceptance and is even successfully used as a prophylactic in manic-depressives. The explanation of its mode of action varies according to the views held about the chemical basis of the disease, and the subject still requires clarification.

New Putative Transmitters

Up to now this survey has been dealing mainly with man-made drugs but there is a section of pharmacology, which Dale used to call 'autopharmacology', which is concerned with highly active body constituents. Progress in the biochemistry of brain constituents has recently been made in many directions: advances in protein chemistry, including enzymology, in lipid chemistry of excitable membranes, in the chemistry of acids like the prostaglandins and nucleic acids, keep modifying our outlook on the function of the brain. However, these fields are usually considered to be the realm of the biochemist, whereas one group of substances has traditionally, since Otto Loewi's time, been largely explored by pharmacologists: that is the field of transmitters, substances formed in neurons and released by them as chemical messengers to another neuron. It may seem arbitrary to single out these substances from other equally essential organic compounds, but recent progress in that field has been what one can only call explosive, and therefore merits preferential treatment.

Acetylcholine and the Monoamines

To deal with developments in chronological order, acetylcholine and the monoamines will be discussed first, followed by aminoacids, and, finally, by peptides. Whereas in the earlier years, it was very difficult to get even acetylcholine accepted as a transmitter of impulses in the brain, the tendency has now overshot in the other direction; a peptide need only be isolated from either intestine or brain, a fluorescent antibody prepared and the tissue searched for fluorescent fibres: if such fibres are found, the substance is added to the growing list of putative transmitters.

The uneven distribution of a substance in the brain shows that it is not a basic constituent of every brain cell, and was, before better means became available, one of the criteria which had to be fulfilled in order to consider a substance as a candidate for a transmitter role.

The uneven distribution of acetylcholine in the brain was demonstrated by MacIntosh in 1941, that of noradrenaline by Vogt in 1954, that of 5-hydroxytryptamine by Amin, Crawford and Gaddum in the same year, and that of dopamine by Carlsson in 1959. The following facts have helped to establish acetylcholine as a central transmitter: there are muscarinic and nicotinic acetylcholine receptors in the CNS, characterized by their respective antagonists; the action of anti-cholinesterases develops slowly after administration, indicating the gradual accumulation of endogenous acetylcholine in the tissue; last, but not least, release has been shown into a cup applied to the cortex and into the cerebral ventricles; it appeared in ventricular perfusates as a result of afferent sensory stimuli or of electrical stimulation of the reticular formation.

The finding by Pletscher, Shore and Brodie (1955) that reserpine causes a disappearance of 5-hydroxytryptamine from the intestine, led to an early recognition that it liberated all three monoamines from all tissues including the brain; if the central effects of reserpine could be attributed to the loss of brain amines, the latter were bound to play a crucial role in mood and behaviour, including motility. The therapeutic use of reserpine in mental disease, though not unsuccessful, was short-lived, since chlorpromazine, discovered almost at the same time, was as effective and lacked the serious side-effects of reserpine. Yet reserpine was already used in mental illness in Hindu Ayurvedic medicine! The main therapeutic value of reserpine at present is in hypertension. It has, however, been, and still is, an invaluable experimental tool in trying to assess the functional role of brain amines.

The hypothesis that the brain amines are transmitters has been strongly supported, first, by their visualization along the whole length of the neuron by fluorescence microscopy, as shown in 1959 by Falck and Hillarp, using a method discovered by Eränkö (1955); secondly, by the demonstration that the monoamines can be released by appropriate electrical stimulation performed either on the whole animal or in brain sections.

One neurological disease has conspicuously profited from the improved knowledge of monoaminergic pathways in the brain, and that is Parkinson's disease. Whereas it was known since 1919 that a destruction of the substantia nigra was the morphological basis of Parkinson's disease, the discovery of the dopaminergic striato-nigral pathway was only possible with the knowledge that dopamine is a central transmitter. With the demonstration by Ehringer and Hornykiewicz (1960) that the striatum contains very little dopamine in these patients, the road was open for a more rational therapy of the disease by giving the dopamine precursor DOPA. The efficacy of the treatment can be improved and the side-effects diminished by the simultaneous administration of an inhibitor of peripheral amino acid decarboxylase. Yet, even this treatment which appears rational is very crude if one considers that one is supplying the uninhibited cholinergic striatal neurons with the lacking dopamine not at the very discrete sites and times at which the body normally delivers it, but by continuously flooding with DA the whole of the brain, including the many regions where it is not wanted.

Histamine

This diamine occurs in small quantities in the brain, particularly in the hypothalamus. There is circumstantial evidence for its role as a transmitter of impulses, but its functional role remains unknown. The study of its distribution is made difficult by the fact that it is present in mast cells which may be quite abundant in the meninges. However, its tissue concentration falls after discrete brain lesions, suggesting an additional localization within neurons.

Amino Acids

It is now certain that a number of amino acids, in addition to playing an important role in brain metabolism and as constituents of proteins, can act as transmitters of impulses. For γ-aminobutyric acid (GABA) and for glycine, this role is well substantiated by findings based on many techniques; their role is inhibitory, as also in accordance with the convulsive action of their specific antagonists, picrotoxin and strychnine. Potential therapeutic usefulness of GABA in epilepsy has been limited by its poor penetration through the blood-brain barrier.

Bird and Iversen (1977) have shown a large reduction in the GABA concentration in many parts of the brain in patients suffering from Huntington's chorea. The atrophic striatum and pallidum were mainly, but not exclusively, affected. Attempted substitution therapy has not, so far, proved successful. Even if the obstacle of the blood-brain barrier can be overcome, the destruction of brain tissue in this condition may stand in the way of a simple replacement therapy.

When applied locally, many amino acids, for example, glutamate, stimulate nerve cells, and glutamate is known to be a transmitter in insects and crustaceans. In the mammal, the role of the stimulating amino acids as transmitters is still uncertain, although glutamate is likely to transmit impulses in some afferent fibres to the spinal cord and to the cerebral cortex, and in pathways from cortex to caudate, dentate gyrus and thalamus.

Peptides

It is, however, in the field of peptides that progress has been most recent, most rapid and most revolutionary. The first 'neuropeptide' to intrigue pharmacologists was 'substance P', isolated from brain and intestine by von Euler and Gaddum in 1931, but its purification posed very great difficulties. These were only resolved in 1970 when it was identified as an undecapeptide by Chang and Leeman. It is interesting that their achievement was the result of a search for corticotrophin releasing factor, and that the guiding bioassay was not the contraction of the ileum or the fall in blood pressure which are the traditional assay methods for substance P, but its sialogogic property. Identification was soon followed by its synthesis. Hypothalamus, septum, substantia nigra and interpeduncular nucleus are rich in substance P, but a group of spinal afferent C-fibres which have their cells of origin in the spinal ganglia, has been of particular interest because it represents an important afferent pain pathway. It must be at least one of the pathways affected by the virus of shingles. When applied electrophoretically, substance P causes excitation of only those dorsal horn neurons that are excited by noxious radiant heat (Henry, 1976). P-containing fibres which end in the substantia nigra stimulate the dopaminergic nigro-striatal pathway.

The next group of peptides to be discussed has a very short history indeed—they are the endogenous ligands for opioid receptors, the enkephalins and endorphins. Their existence was postulated by a number of workers, and Hughes, Smith, Kosterlitz, Fothergill, Morgan and Morris (1975) indeed found two pentapeptides in brain, which they named met-enkephalin and leu-enkephalin, which bound to opioid receptors, mimicked the actions of morphine on isolated tissues, and were soon shown to have fleeting analgesic activity. That the endogenous ligand might be a peptide had already been suggested in 1974 by Terenius and Wahlström. They extracted brain and CSF and found a heat-stable compound which displaced dihydromorphine from binding sites and was not soluble in organic solvents.

While work on the brain was proceeding, Goldstein and co-workers (*see* Goldstein, 1976) started to analyse pituitary extracts where they found an opioid peptide of the approximate molecular weight of 3000 (the equivalent of 25–30 amino acids). Among the large pituitary peptides of known structure was one called β-lipotropin identified and sequenced in 1965 by Li, Barnafi, Chrétien and Chung. It mobilized fatty acids from fat tissue and was now seen to contain, in its chain of 91 amino acids, the sequence of met-enkephalin (fragment 61-65). Furthermore, it was easily cleaved to produce the fragment 61-91. Goldstein and Li (*see* Goldstein, 1976) joined forces and found that the peptide 61-91 was a potent opioid, whereas the parent peptide had no such activity. The fragment 61-91 was given the name β-endorphin. In the same period, the sequence of 61-91 was also isolated from lipotropin by Smyth, Snell and Massey and given the name C-fragment. Whereas all these shorter fragments are analgesic, the action of the pentapeptides is short-lived, since they are subject to hydrolysis by peptidases. They can be stabilized against hydrolysis by chemical modification without losing their analgesic action: alas, these stabilized compounds acquire the capacity of producing tolerance and dependence!

The role in nervous activity of the enkephalins and of β-endorphin may be very different. Although met-enkephalin and β-endorphin are fragments of β-lipotropin, only β-endorphin is known to be stored within, and released from, the precursor β-lipotropin; this forms a part of an even larger storage peptide of about 260 amino acids (called 31 K peptide) which also contains the sequence for ACTH. As a result, the cells from the pars distalis and pars intermedia which produce ACTH also contain the β-endorphin sequence, and both peptides are released together by these cells *in vitro* and also *in vivo*. By radioimmunoassay β-endorphin has also been found in the brain, and here, like the enkephalins, it is stored within neurons, but together with ACTH. Its distribution within the brain is quite different from that of the enkephalins. The latter are found in high concentration in striatum, pallidum and substantia nigra. Furthermore, Hökfelt, Ljungdahl, Terenius, Elde and Nilsson (1977), using immunohistochemical methods, observed met-enkephalin in cell bodies and terminals of the periaqueductal grey, the nucleus raphe magnus, the trigeminal substantia gelatinosa and the dorsal horn of the cord. These findings suggest an involvement of the enkephalins in pain sensation.

In contradistinction, cerebral β-endorphin immunofluorescence is restricted mainly to the olfactory bulb and the periarcuate region of the hypothalamus. However, axons originating in the hypothalamus may be traced for long distances into other parts of the brain.

There are several facts which suggest that the enkephalins may be transmitters of impulses: electrical stimulation releases them from the myenteric plexus, and potassium from striatal synaptosomes. The free peptides are rapidly destroyed by peptidases. Rapid inactivation either by destruction or re-uptake is, of course, essential for a substance to perform transmitter action. β-Endorphin, on the other hand, is not broken down very rapidly. It can be found in blood in very low (and apparently physiologically inactive) concentrations whenever ACTH is being released; in the CSF, however, its concentration seems to be correlated with certain clinical states or manipulations. Thus it is likely that analgesia produced by electrical stimulation of the central grey is mediated by β-endorphin: Akil, Watson, Levy and Barchas (1978) found that during stimulation of electrodes which were being implanted into patients with intractable pain, the β-endorphin content of the CSF obtained from the third ventricle rose whenever pain relief was experienced. Similarly, electro-acupuncture performed on patients with back pain led to a rise in endogenous opioid content of lumbar CSF; however, the test would not have discriminated between β-endorphin and enkephalins. The same is true of observation on CSF opioids in different forms of pain: low concentrations, below the norm established in healthy volunteers, are frequent in patients with chronic 'neurogenic' as contrasted with 'psychogenic' pain (*see* Terenius, 1978). It is likely that phantom pain is caused by a subnormal production of endogenous opioids, perhaps resulting from total loss of afferent impulses. Whether or not the enkephalins, like β-endorphin, are derived from a large precursor, is unknown. It is, however, certain that the enkephalins are not produced by cleavage of β-lipotropin found in the pituitary, since Cheung and Goldstein (1976) have shown that hypophysectomy has no effect on the concentration of enkephalins in the brain.

Whereas there is convincing evidence that β-endorphin and enkephalins play a role in pain perception, these substances may have many other actions. One way of discovering such actions is the administration of the specific morphine antagonist naloxone. If it is given to a man or animal in perfect health and under stress-free environmental conditions, the drug appears to produce little or no effect at all. However, given to an anæsthetized animal which has been subjected to stress, there is a rise in blood pressure (Dashwood and Feldberg, 1979), as there is if naloxone is injected a few hours after an injection of morphine. In man suffering from acute pain (as after a tooth extraction), the pain may become worse. Grevert and Goldstein (1977) studied the pain threshold to ischæmia in volunteers. They found the pain threshold unaltered by naloxone but tension and anxiety increased.

With this knowledge, it is obvious that endogenous opioids may be suspected to play a role in mental disease. Only few observations on the use of naloxone are as yet available: the claim that hallucinations are reduced by its administration seems to be valid only for a very restricted number of patients. In mania, there was some success in 4 of 12 cases, and these were the subjects with the most extreme abnormalities of behaviour (Judd, Janowsky, Segal and Huey, 1978). Since even in normal controls drowsiness follows the high dose (20 mg) used, the effect may be non-specific.

If there are innumerable unanswered questions in the enkephalin and β-endorphin field, there are even more uncertainties about other peptides now considered to affect brain activity. It is a heterogenous group: there are, first, vasopressin and the trophic hormones of the anterior pituitary, secondly, the substances which cause or inhibit the release of these hormones, and finally peptides unrelated to the pituitary which, like substance P and the enkephalins, are found both in the intestine and in the CNS.

Group one is mainly of endocrinological interest. However, as first shown by de Wied (1969), ACTH and some ACTH fragments (containing the sequence 4–10) have extra-adrenal effects on processes of memory: extinction of acquired behaviour and its acquisition and retention are modified by direct action of these peptides on the CNS. Similar modifications are produced by vasopressin, but the effect of single injections is peculiar in that it lasts for days. Some self-perpetuating secondary effect may be set in motion by the hormone.

Are these findings pharmacological artefacts or are they of physiological importance? The latter view is favoured by some recent observations, which show that ACTH may not only reach the brain in minute quantities from the systemic circulation, but may originate from two other sources: antiserum has shown the presence of ACTH (with β-lipotropin) in hypothalamic neurons, from which its release is a possibility. Furthermore, the hypophyseal portal vessels, which carry blood from hypothalamus to distal lobe, are now known not to be the only vascular connection between pituitary and brain. A subependymal plexus covers the infundibular stalk and contains blood flowing from pituitary to median eminence. Its importance in transporting pituitary hormones to brain structures was demonstrated by Oliver, Mical and Porter (1977); they introduced a cannula into a long portal vessel directing its tip towards the hypothalamus. They found high concentrations of LH, TSH, prolactin, ACTH, α-MSH and vasopressin in this blood, indicating that all pituitary hormones have direct access to the brain and may therefore influence its activity.

The second group, known as the releasing or release-inhibiting factors, includes substances such as TRH (thyrotrophin-releasing hormone), and somatostatin (a factor inhibiting growth hormone release). These substances, conventionally called 'hormones' or 'factors', occur in neurons of the median eminence and basal hypothalamus, where they effect the neural control of the release of hormones from the anterior pituitary. By definition these 'factors' are no different from any transmitter which is released on to a gland cell rather than on to another neuron. Immunofluorescence has shown that their terminals are not restricted to the median eminence, but occur in other parts of the brain. Neurons with the same immunological characteristics occur in the intestine, and somatostatin reactivity is found in the pancreas.

To start with TRH, one region of the brain of the rat in which Hökfelt, Fuxe, Johansson, Jeffcoate and White (1975) showed the presence of fibres giving the immunofluorescence to TRH, is the nc. accumbens. Heal and Green (1979) showed that injection into this region of a few μg of TRH causes increased locomotion in the rat, and this is accompanied by a release of DA; a similar injection into the caudate has no effect on locomotion or DA release, nor are there fluorescent fibres to be found in that structure after treatment with fluorescent antibody to TRH. It is conceivable that the function of these fibres in the nc. accumbens is the control of DA release.

TRH has been applied iontophoretically and shown to modify the electrical activity of neurons throughout the brain; it also enhances the responses to locally applied ACh. There is no doubt that it shares with many peptides an activity on nerve cell membranes, but since its role in normal function must depend on where it is, in fact, released, it will take quite some time till a clear picture about its importance can emerge.

In contrast to TRH, somatostatin appears to have only inhibitory functions: the hormone made in the median eminence diminishes the release of growth hormone, that manufactured in the D-cells of the pancreas is probably responsible for the reduction in secretion of both insulin and glucagon; however, its administration is also known to reduce the production of secretin, and this may be one of the functions of the peptide manufactured in the gut. Another might be the reduction of ACh release from the myenteric plexus. It is difficult to conceive somatostatin ever to be called upon to act as a circulating hormone affecting a large number of organs simultaneously: its function is more likely to be that of an inhibitory local hormone or transmitter.

A further complication in the interpretation of the data has arisen through the observation by Hökfelt, Elfvin, Elde, Schultzberg, Goldstein and Light (1977) that immunoreactivity to somatostatin is found in noradrenergic cells of the guinea pig's cœliac and inferior mesenteric ganglia. Is this an example, in a mammal, of an exception to Dale's concept of one-neuron one-transmitter? To show more convincingly that somatostatin could be a transmitter in an adrenergic neuron, it would, of course, be necessary to show its occurrence at nerve terminals as well as in the perikaryon of noradrenaline containing cells. 'Vasoactive intestinal peptide', belonging to the last group of peptides to be discussed, has also been found by the Swedish group in some adrenergic perikarya of the pre-aortic ganglia of the guinea pig. The authors are well aware that immunoreactivity is fraught with technical pitfalls, but our thinking in this field may have been too restrictive.

This last group of peptides seems to be steadily growing, but only five compounds will be briefly discussed: gastrin, vasoactive intestinal peptide, neurotensin, bombesin and angiotensin. As far as is known, they all lack connection with the pituitary gland; with the exception of angiotensin, they were discovered in the gastrointestinal tract, but can all be shown by immunofluorescence to occur in the brain.

In the gastrointestinal tract, their release is correlated with different phases of the gastrointestinal responses to food intake, and their concentration seems to change in pathological states like cœliac disease. The role in the brain of the five peptides is very incompletely known. Angiotensin injected into the hypothalamus or given intravenously induces drinking (Fitzsimons, 1972), and it is very likely that the control of thirst is a function of cerebral and peripherally produced angiotensin II. Gastrin-like activity is very widespread in the brain, with the highest concentration in the amygdala, and cell bodies in the hippocampus, but so far no possible function seems to have been suggested. Vasoactive peptide (VIP), being a vasodilator, may affect brain vessels as it undoubtedly influences intestinal blood flow. Cells giving immunofluorescence to VIP have been found in the amygdala and the neocortex. Neurotensin is another hypotensive peptide, isolated together with substance P from bovine hypothalamus by Carraway and Leeman in 1973, is thought to be involved in temperature regulation and to be antagonized by TRH. It has been traced in a pathway originating in perikarya of the amygdala and having its terminals in the nucleus interstitialis of the stria terminalis, the same pathway in which enkephalin had been earlier found by immunofluorescence. It is, however, not clear whether or not the two peptides exist in the same fibres.

Bombesin was discovered in 1972 by Anastasi, Erspamer and Bucci in the skin of frogs, and it came quite as a surprise that it occurs in human nerve fibres of the gastrointestinal tract and of the hypothalamus. More surprising still was the finding (Brown, Rivier and Vale, 1977) that on intracisternal administration it is ten-thousand times more active than neurotensin in lowering the temperature of rats kept at 4° C. One ng injected into a 200 g rat was fully effective.

These observations illustrate the unsatisfactory state of our insight into the possible role of these peptides in brain function and constitute a challenge for future research.

REFERENCES

Akil, H., Watson, S. J., Levy, R. M. and Barchas, J. D. (1978) β-Endorphin and other 31 K fragments: pituitary and brain systems. *Developments in Neuroscience*, **4**, 123-158.

Amin, A. H., Crawford, T. B. B. and Gaddum, J. H. (1954) The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *Journal of Physiology, London*, **126**, 596-618.

Anastasi, A., Erspamer, V. and Bucci, M. (1972) Isolation and amino acid sequences of alytesin and bombesin, two analogous active tetradecapeptides from the skin of European discoglossid frogs. *Archives of Biochemistry and Biophysics*, **148**, 443-446.

Bennett, A. E. (1940) Preventing traumatic complications in convulsive shock therapy by curare. *Journal of the American Medical Association*, **114**, 322-324.

Bird, E. D. and Iversen, L. L. (1977) Neurochemical findings in Huntington's chorea. *Essays in Neurochemistry and Neuropharmacology*, **1**, 177-195.

Brown, M., Rivier, J. and Vale, W. (1977) Bombesin: potent effects on thermoregulation in the rat. *Science*, **196**, 998-1000.

Buttle, G. A. H., Stephenson, D., Smith, S., Dewing, T. and Foster, G. E. (1937) Treatment of streptococcal infections in mice with 4,4′-diaminodiphenylsulphone. *Lancet*, **i**, 1331-1334.

Carlsson, A. (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacological Reviews*, **11**, 490-493.

Carraway, R. and Leeman, S. E. (1973) The isolation of a new hypotensive peptide, neurotensin, from bovine hypothalami. *Journal of Biological Chemistry*, **248**, 6854-6861.

Chang, M. M. and Leeman, S. E. (1970) Isolation of a sialogogic peptide from bovine hypothalamic tissue and its characterization as substance P. *Journal of Biological Chemistry*, **245**, 4784-4790.

Cheung, A. L. and Goldstein, A. (1976) Failure of hypophysectomy to alter brain content of opioid peptides (endorphins). *Life Sciences*, **19**, 1005-1008.

Dashwood, M. R. and Feldberg, W. (1979) Central inhibitory effect of released opiate peptides on adrenal medulla, revealed by naloxone in the cat. *Journal of Physiology, London*, **290**, 22-23P.

Delay, J., Deniker, P. and Harl, J.-M. (1952) Traitement des états d'excitation et l'agitation par une méthode médicamenteuse dérivée de l'hibernothérapie. *Annales Médico-psychologiques*, **110**, 267-273.

de Wied, D. (1969) In: *Frontiers in Neuroendocrinology*. Edited by W. F. Ganong and L. Martini. London: Oxford University Press, pp. 97-140.

Domagk, G. (1935) Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Deutsche Medizinische Wochenschrift*, **61**, 250-253.

EHRINGER, H. and HORNYKIEWICZ, O. (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klinische Wochenschrift*, **38**, 1236–1239.

ERÄNKÖ, O. (1955) Distribution of fluorescent islets, adrenaline and noradrenaline in the adrenal medulla of the cat. *Acta Endocrinologica*, **18**, 180–188.

EULER, U. S. VON and GADDUM, J. H. (1931) An unidentified depressor substance in certain tissue extracts. *Journal of Physiology, London*, **72**, 74–87.

FALCK, B. and HILLARP, N.-Å. (1959) On the cellular localization of catecholamines in the brain. *Acta Anatomica*, **38**, 277–279.

FITZSIMONS, J. T. (1972) Thirst. *Physiological Reviews*, **52**, 468–561.

GOLDSTEIN, A. (1976) Opioid peptides (endorphins) in pituitary and brain. *Science*, **193**, 1081–1086.

GREEN, A. R. (1978) Repeated exposure of rats to the convulsant agent flurothyl enhances 5-hydroxytryptamine and dopamine-mediated behavioural responses. *British Journal of Pharmacology*, **62**, 325–331.

GREVERT, P. and GOLDSTEIN, A. (1977) Effects of naloxone on experimentally induced ischaemic pain and on mood in human subjects. *Proceedings of the National Academy of Sciences USA*, **74**, 129–194.

GRIFFITH, H. R. and JOHNSON, G. E. (1942) The use of curare in general anesthesia. *Anesthesiology*, **3**, 418–420.

HEAL, D. J. and GREEN, A. R. (1979) Administration of thyrotropin releasing hormone (TRH) to rats releases dopamine in n. accumbens but not n. caudatus. *Neuropharmacology*, **18**, 23–31.

HENRY, J. L. (1976) Responses of dorsal horn units in cat spinal cord to some putative transmitters and to cutaneous stimulation. *British Journal of Pharmacology*, **57**, 435P.

HÖKFELT, T., ELFVIN, L. G., ELDE, R., SCHULTZBERG, M., GOLDSTEIN, M. and LIGHT, P. (1977) Somatostatin-like immunoreactivity in principal ganglion cells of some sympathetic ganglia. *Proceedings of the National Academy of Sciences USA*, **74**, 3587–3591.

—— FUXE, K., JOHANSSON, O., JEFFCOATE, S. and WHITE, N. (1975) Distribution of thyrotropin-releasing hormone (TRH) in the central nervous system as revealed with immunohistochemistry. *European Journal of Pharmacology*, **34**, 389–392.

—— LJUNGDAHL, Å., TERENIUS, L., ELDE, R. and NILSSON, G. (1977) Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: enkephalin and substance P. *Proceedings of the National Academy of Sciences USA*, **74**, 3081–3085.

HUGHES, J., SMITH, T. W., KOSTERLITZ, H. W., FOTHERGILL, L. A., MORGAN, B. A. and MORRIS, H. R. (1975) Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature, London*, **258**, 577–579.

JUDD, L. L., JANOWSKY, D. S., SEGAL, D. S. and HUEY, L. Y. (1978) Naloxone related attenuation of manic symptoms in certain bipolar depressives. *Developments in Neuroscience*, **4**, 173–174.

LABORIT, H., HUGUENARD, P. and ALLUAUME, R. (1952) Un nouveau stabilisateur végétatif, le 4560 RP. *Presse Médicale*, **60**, 206–208.

LI, C. H., BARNAFI, L., CHRÉTIEN, M. and CHUNG, D. (1965) Isolation and amino-acid sequence of β-LPH from sheep pituitary glands. *Nature, London*, **208**, 1093–1094.

MACINTOSH, F. C. (1941) The distribution of acetylcholine in the peripheral and the central nervous system. *Journal of Physiology, London*, **99**, 436–442.

MEDUNA, L. VON and FRIEDMAN, E. (1939) Convulsive-irritative therapy of psychoses; survey of more than 3000 cases. *Journal of the American Medical Association*, **112**, 501–509.

MILLICHAP, J. G. (1968) Drugs in management of hyperkinetic and perceptually handicapped children. *Journal of the American Medical Association*, **206**, 1527–1530.

OLIVER, C., MICAL, R. S. and PORTER, J. C. (1977) Hypothalamic-pituitary vasculature: evidence for retrograde blood flow in the pituitary stalk. *Endocrinology*, **101**, 598–604.

PLETSCHER, A., SHORE, P. A. and BRODIE, B. B. (1955) Serotonin release as a possible mechanism of reserpine action. *Science*, **122**, 374–375.

SCHOU, M., JUEL-NIELSEN, N., STRÖMGREN, E. and VOLDBY, H. (1954) The treatment of manic psychoses by the administration of lithium salts. *Journal of Neurology and Psychiatry*, **17**, 250–260.

SMYTH, D. G., SNELL, C. R. and MASSEY, D. E. (1978) Isolation of the C-fragment and C'fragment of lipotropin from pig pituitary and C-fragment from brain. *Biochemical Journal*, **175**, 261–270.

SULSER, F., VETULANI, J. and MOBLEY, P. L. (1978) Mode of action of antidepressant drugs. *Biochemical Pharmacology*, **27**, 257–261.

TERENIUS, L. (1978) The implications of endorphins in pathological states. *Developments in Neuroscience*, **4**, 143–158.

—— and WAHLSTRÖM, A. (1974) Inhibitor(s) of narcotic receptor binding in brain extracts and cerebrospinal fluid. *Acta Pharmacologica et Toxicologica*, **35**, Supplement, p. 55.

VOGT, M. (1954) The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *Journal of Physiology, London*, **123**, 451–481.

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QUANTITATIVE ANALYSIS OF STANCE IN LATE CORTICAL CEREBELLAR ATROPHY OF THE ANTERIOR LOBE AND OTHER FORMS OF CEREBELLAR ATAXIA[1]

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INTRODUCTION

THE cerebellum has three functional subsystems characterized by their input: the vestibulo-cerebellum receiving afferents from the vestibular organs; the spino-cerebellum, mainly supplied by afferents from the spinal cord; and the ponto-cerebellum which gets its main input from the neocortex via the pontine nuclei (Brodal, 1969).

Anatomically, the flocculonodular lobe and the posterior part of the uvula form the vestibulo-cerebellum; the anterior vermis and paravermis of the anterior lobe form the spino-cerebellum; and the cerebellar hemispheres form the ponto-cerebellum (Dow and Moruzzi, 1958).

Localized lesions of these cerebellar subsystems in various animals have been shown to cause characteristic symptoms: the flocculonodular syndrome (consisting of equilibrium disturbances and nystagmus); the neocerebellar syndrome (mainly limb ataxia and hypotonia); and the anterior lobe syndrome (increased myotatic and postural reflexes). The literature (for references *see* Dow and Moruzzi, 1958; Fields and Willis, 1970; Dow, 1969) contains almost no quantitative reports concerning the influence of these functional cerebellar subsystems upon the control of upright stance either in primates or in man (Njiokiktjien and van Parys, 1976). One reason might be that human cerebellar diseases restricted to particular functional parts of the cerebellum are rare.

For the present study *three groups of patients* with restricted cerebellar lesions

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were selected for quantitative analyses aimed at elucidating the functional organization of the cerebellar stabilization of posture:

(1) late cortical atrophies of the anterior lobe;
(2) tumours of a neocerebellar hemisphere;
(3) tumours limited to the vestibulo-cerebellum.

Late cortical cerebellar atrophies of the anterior lobe were selected because surgical interventions restricted to the vermis and paravermis of the anterior lobe are extremely rare. Few cases only have been published (Kononova, 1926; Brown, 1949), one of which presented signs of brain-stem involvement. However, in late cortical cerebellar atrophy, as described extensively by Marie, Foix and Alajouanine in 1922 (atrophie cérébelleuse tardive à prédominance corticale), the lesions are sufficiently limited to the vermal and paravermal part of the anterior lobe. The disease, which occurs mostly in chronic alcoholics, proved to be remarkably stereotyped in its clinical and pathological manifestations (Victor and Ferrendelli, 1970). Victor, Adams and Mancall (1959) gave a detailed account of the pathological changes and their topography in 50 cases of this form of cerebellar atrophy. The changes consisted in a degeneration of the cerebellar cortex, particularly of the Purkinje cells, and were strikingly restricted to the anterior and superior aspects of the vermis and, in advanced cases, to the paravermal parts of the anterior lobe, regions where the spinal afferents end (Grant, 1962*a*, *b*).

PATIENTS

Group 1 with an anterior lobe syndrome comprised 13 patients, 9 men and 4 women, with the clinical symptomatology of late cortical cerebellar atrophy (mean age 51, SD ± 7.5 years). All patients had marked gait disturbances with a characteristic stiff-legged and wide-based walking. There was only mild or no ataxia of the upper limbs, with minor or no changes in handwriting. No hypotonia of the limbs was observed in these patients. Some had spontaneous and gaze nystagmus. Eye tracking and optokinetic nystagmus were disturbed in 7 out of 13 patients as earlier described by Dichgans, von Reutern and Römmelt (1978). Neuropathies were absent with one exception. Other relevant clinical features are summarized in Table 1. All except one patient had a long history of alcohol misuse and there was no family history of ataxic disorders or other neurological deficits in any of these patients.

Group 2 with a neocerebellar syndrome comprised 6 patients, 3 men and 3 women. They had tumours restricted to one cerebellar hemisphere as indicated by preoperative computerized tomography and the surgeon's report. Midline structures were never invaded. Further clinical information is summarized in Table 2.

Group 3. Patients with localized lesions in the vestibulo-cerebellum are rare. On the basis of neurosurgical reports we selected 2 patients with a medulloblastoma of the posterior vermis involving the nodulus. The boys were 15 and 16 years old when

TABLE 1. PATIENTS WITH LATE CORTICAL CEREBELLAR ATROPHY

Patient	*Age*	*Sex*	*Duration of illness at first exam.*	*Alcohol*	*Nystagmus*	*Speech disturbance*	*Reflexes*	*Other neurological features*
1	50	M	1 yr.	++	Gaze nyst. pursuit ↓ OKN ↓	Slight	++	—
2	55	F	5 yrs.	+	SPN+	Slight	++	Dysdiadochokinesis of left arm
3	50	M	1 yr.	++	Normal	Slight	++	—
4	54	M	About 3 yrs.	++	Normal	None	+	Slight neuropathy
5	62	F	Several yrs.	+	Pursuit ↓ OKN ↓	None	+	—
6	60	F	7 yrs.	None	Gaze nyst. OKN ↓	Slight	+	Slight ataxia of both arms
7	58	M	Several yrs.	+	Gaze nyst. pursuit ↓ OKN ↓	Slight	++	—
8	38	M	2 yrs.	++	Pursuit ↓ OKN ↓	None	+	Dysdiadochokinesis (bilateral slight)
9	51	M	6 months	++	SPN+	None	++	—
10	56	M	1 yr.	++	Normal	None	+	—
11	43	M	1 yr.	++	Pursuit ↓ OKN ↓	None	++	One attack of delirium tremens
12	43	M	5 weeks	++	Normal	None	++	—
13	42	M	Few weeks	++	Gaze nyst. pursuit ↓ OKN ↓	None	++	—

SPN = spontaneous nystagmus. OKN = optokinetic nystagmus.

TABLE 2. PATIENTS WITH CEREBELLAR HEMISPHERICAL LESIONS (WITHOUT INVOLVEMENT OF MIDLINE STRUCTURES)

Patient	*Sex*	*Age*	*Diagnosis*	*Time between opn. and recording*	*Neurological defects*
1	M	41	L. hemispherical astrocytoma with small cyst, resection of parts of lobulus semilunaris and lobulus biventer	3 weeks, 11 weeks and 1 year	Gaze nystagmus to the L. SPN to the L. OKN to the R. ↓. Fixation suppression ↓. Slight ataxia of L. arm
2	F	23	Gangliocytoma of the R. hemisphere; resection of lobulus biventer and semilunaris	3 weeks	Minor gait ataxia; R.-sided ataxia and dysdiadochokinesis of extremities, abducens paresis on L.
3	F	27	L. hemispherical tentorium-meningeoma; only minor resection in region of sinus transversus	2 weeks	Gaze nystagmus to the L.; SPN to the L. Only slight ataxia of L. arm
4	M	51	R. hemispherical astrocytoma. Only parts of lobulus biventer resected	4 weeks	Gaze nystagmus to both sides; pronounced ataxia of R. arm
5	M	50	Spongioblastoma of the L. hemisphere. Large resections of lobulus biventer and semilunaris	4 months	Gaze nystagmus to both sides; SPN to R.; enhanced symmetrical tendon reflexes; hypotonia, dysdiadochokinesis and ataxia of L. limbs
6	F	27	Astrocytoma of L. hemisphere. Total resection of lobulus biventer, parts of lobulus semilunaris superior and inferior	4 weeks	Ataxia of L. limbs; fixation suppression ↓

SPN = spontaneous nystagmus. OKN = optokinetic nystagmus.

they developed signs of increased intracranial pressure due to occlusion hydrocephalus. Recordings were obtained three and ten weeks respectively after operation including a ventriculo-atrial shunt. Both exhibited spontaneous and gaze nystagmus and severely disturbed ocular pursuit. Because of their marked disturbance of equilibrium only short recordings were possible.

METHODS

Measurement of Body Sway

Subjects stood on a commercially available force-moment measuring platform (Kistler Ch-8408 Winterthur, Type 9261A). The platform was supported at each of its corners by a piezo-electric force transducer which measured locally three orthogonal forces (anterior-posterior, lateral and vertical). By summing the outputs of these four transducers in charge amplifiers the three components of the subject's reaction forces on the platform and the reaction moment about the lateral and antero-posterior axes were obtained.

The displacement of the resultant centre of force was calculated from these force components and their respective moments using an analog circuitry (for further details *see* Dichgans, Mauritz, Allum and Brandt, 1976). The displacement of the centre of force is equivalent to the displacement of the centre of gravity only at very low frequencies. At higher frequencies dynamic components due to body inertia add to the static forces and account for 50 per cent at 0.5 Hz, whereas they are less than 10 per cent at 0.2 Hz (Gurfinkel, 1973). Our recording technique therefore measured not the net displacement of the centre of gravity but the torque about the ankles and the reaction forces at the feet. For an estimation of relative movements between body segments, hip and head tilts were recorded by an electronic goniometer (Schaewitz Engineering, Model LSRP, frequency range 0–20 Hz), which was fastened to a belt around the subject's waist or head.

In some cases, the angle of the ankle was monitored by a potentiometer connected to a hinge, one arm of which was strapped to the leg of the subject, the other to the foot.

Data Recording

For later processing, data about antero-posterior (y) and lateral (x) displacements of the centre of force, which are measured by the platform (fig. 1A), and hip and head movements, as well as ankle angle and EMG were stored on FM magnetic tape. Displacements of the centre of force and EMG were monitored during the experiment. Subjects stood on the platform with heels separated 4 cm and feet splayed at an angle of approximately 30 degrees. They were instructed to remain as upright as possible and to refrain from any voluntary movements during the two-minute recording trials. If the pre-set position of the feet had changed, the measurement was discarded.

Data Analysis

For *Fourier analysis* of postural sway components we used a digital computer (IBM 1130) and a program developed by J. H. J. Allum (*see* Allum, Dietz and Freund, 1978 and Dichgans *et al.*, 1976). After analog to digital conversion with a sample rate of 100/s, 37 second segments were analysed. x and y components were separately passed through a digital Butterworth lowpass filter by which all the oscillations above 12 Hz were damped to eliminate noise and tape flutter. In a few instances a commercially available on-line Fast-Fourier analyser (Nicolet 444A FFT computing spectrum analyser) was used.

Calculation of Sway Parameters

In order to obtain a complete description of standing stability as recorded by the measuring platform, several other sway parameters were computed (Hufschmidt, 1977). It was not possible to place

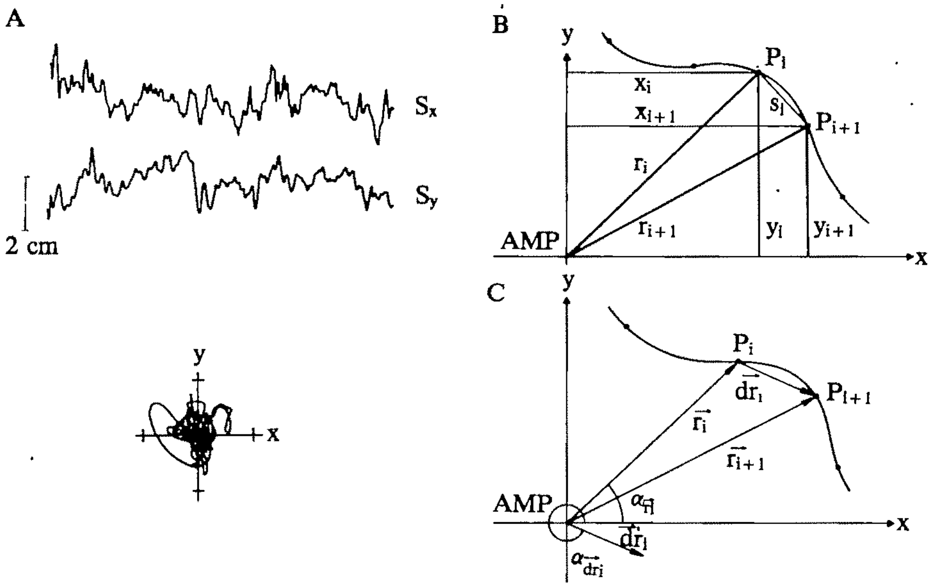

FIG. 1. Scheme illustrating the calculation of body sway parameters and sway histograms. A, *above*, Sway components of the centre of force displacement in the lateral (Sx) and anterior-posterior direction (Sy). *Below*, x-y plot of the centre of force-displacement. B, Calculation of sway parameters. The arithmetic mean point (AMP) is the average of all x_i, x_{i+1} and all y_i, y_{i+1} co-ordinates. The mean amplitude (MA) of force displacements is obtained by averaging all r_i, r_{i+1} from this AMP. The length of the sway path (SP) is the sum of the secants s_i, s_{i+1} during the measuring period. C, Calculation of sway histograms. For position histograms r_i, r_{i+1} are summed in 10 degree intervals. Sway direction histograms are obtained by summing the secants in 10 degree intervals and plotting the 36 points from the centre, i.e. the AMP.

the different subjects so that the average vertical projection of their centre of gravity on the platform was identical, even if they had the same pre-set feet position. Therefore, so as to normalize the data, the *arithmetic mean point* (AMP) of the sway path was calculated for each experiment (fig. 1B). All the other parameters were related to this AMP.

The *mean amplitude* (MA) of force displacements describes the average postural deviation from an ideal vertical projection of the centre of gravity. It was calculated as follows: every 30 ms co-ordinates of the sway path were sampled (x_i and y_i in fig. 1B). Then the average radius r was calculated as the average distance between AMP and the measuring points P_i (fig. 1B).

$$MA = \frac{1}{n}\sum_{i=1}^{n} r_i = \frac{1}{n}\sum_{i=1}^{n} \sqrt{(x_i^2+y_i^2)}$$

The length of the curve the centre of force describes in one minute was called the *sway path* (SP). It is the sum of the secants s_i between the 1233 measuring points P_i, P_{i+1}, etc. (fig. 1B) and was calculated according to the following equation:

$$SP = \frac{1}{T_m}\sum_{i=1}^{n-1} s_i = \frac{1}{T_m}\sum_{i=1}^{n-1} \sqrt{\{(x_{i+1}-x_i)^2+(y_{i+1}-y_i)^2\}}$$

T_m = measuring period in minutes; n = 1233.

In the SP measurement the dynamic component (force moment) is more strongly represented than in the mean amplitude.

Sway Histograms

Two kinds of graphical presentations were elaborated to describe the positional and directional distribution of postural sway. The distribution of positions in relation to AMP and the distribution of sway directions were calculated as schematically plotted in fig. 1c. For the calculation of the *position histogram* the distances from AMP (r_i) are summed up over angle intervals of 10 degrees. The summed r_i within each of the 36 intervals represents one point on the graph. Points are linked to form the position histogram (*see* figs. 4 and 8). In a similar way, the sway path vectors (dr_i) are summed up in 36 angle intervals and plotted from the origin of the co-ordinate system as indicated in fig. 1c. The resulting sway *direction histogram* as opposed to the sway position histogram again contains more information about force moments and therefore the dynamic aspects of sway.

RESULTS

1. *Late Cortical Cerebellar Atrophy*

(a) *Characteristics of the spontaneous postural tremor.* The 13 patients within this group invariably showed a regular fore-aft oscillation with an average frequency of 3.0 ± 0.5 Hz (*see* Table 3), the amplitude of which waxed and waned irregularly and showed a large inter-individual variance. A slower oscillation was seen mainly in the lateral direction. The difference between the fore-aft and lateral sway component is exemplified in fig. 2. Whereas the power spectrum—especially in the low frequency range—varies greatly in normals (Dichgans *et al.*, 1976; Mauritz, Dichgans, Allum and Brandt, 1975); patients with anterior lobe atrophies exhibit this very constant and probably specific frequency peak at 3 Hz. The intra-individual variance is extremely low as may be seen from the five recordings obtained on subsequent days from Patient 2, plotted in fig. 2.

TABLE 3. FREQUENCY PEAKS IN PATIENTS WITH LATE CORTICAL CEREBELLAR ATROPHY

		High frequency peak (a.-p.)			*Low frequency peak (lat.)*		
Patient	*Age*	*EO* *Hz*	*EC*	*Ampl. ratio* $\frac{EC}{EO}$	*EO* *Hz*	*EC*	*Ampl. ratio* $\frac{EC}{EO}$
1	50	3.4	3.0	6.8	0.6	0.4	9.3
2	55	3.0	3.0	1.0	0.65	0.6	1.5
3	50	2.7	2.9	30.0	—	0.46	1.0
4	54	2.2	2.6	11.0	0.3	0.4	4.3
5	62	2.8	2.5	1.2	0.5	0.5	3.4
6	60	3.1	3.2	16.0	0.65	0.7	6.0
7	58	3.0	3.0	1.0	0.5	0.48	5.0
8	38	—	3.0	$\gg$ 1.0	—	—	—
9	51	4.0	3.6	14.0	0.42	0.5	16.0
10	56	3.4	3.6	2.9	0.35	0.42	4.5
11	43	3.0	2.8	3.0	0.45	0.3	2.5
12	43	—	2.0	$\gg$ 1.0	0.7	0.7	10.4
13	42	3.6	3.6	7.2	—	—	—
Mean	51	3.1	3.0	—	0.51	0.50	—
SD	7.5	0.5	0.5	—	0.14	0.13	—

EO = eyes open. EC = eyes closed.

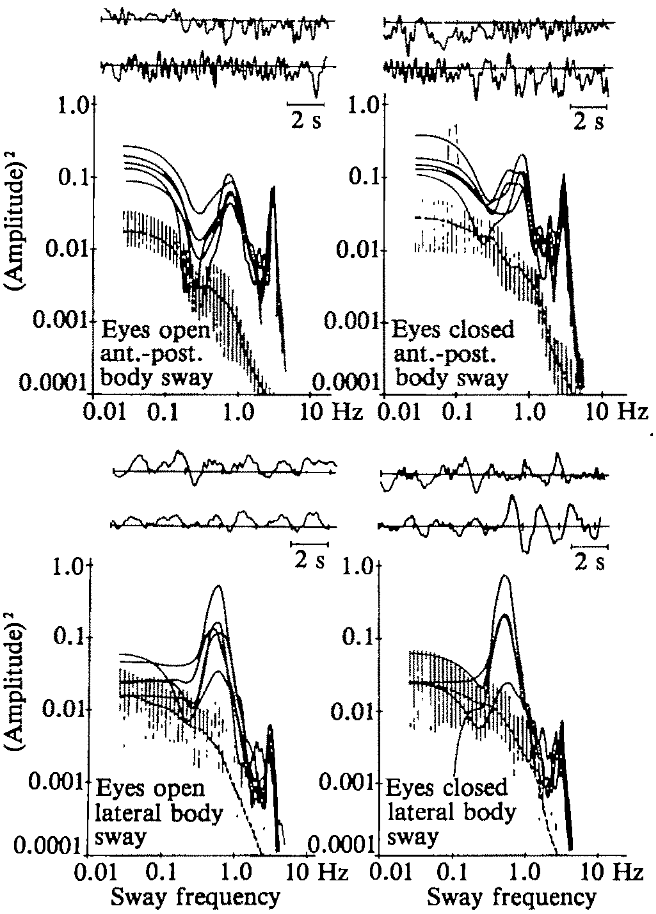

FIG. 2. Fourier power spectra of sway in a patient with late cortical cerebellar atrophy (Patient 2) for the anterior-posterior (*upper half*) and the lateral direction (*lower half*) during eyes open (*left side*) and eyes closed (*right side*). At the top are segments of the original recording. Recordings obtained on five consecutive days are shown and compared to the average (dotted line) and the range of 15 normals (shaded area). The specific 3 Hz frequency peak is seen mostly in the antero-posterior direction, whereas the nonspecific peak around 0.7 Hz is more pronounced in the lateral direction.

In the original registration of the lateral force component (lower half of fig. 2) an additional frequency peak can be observed below 1 Hz. This peak (average 0.5 ± 0.13 Hz) is also frequently seen in cerebellar patients but is less specific since, regardless of the site of the lesion, it is observed in most unstable patients and may be recorded even in visually destabilized normals (Dichgans *et al.*, 1976). The low frequency peak is not as well reproduced during subsequent sessions (fig. 2). Whereas the 3/s peak is most prominent in the fore-aft component, the low frequency peak is generally higher in the lateral. This points to an independent control of body equilibrium in the anterior-posterior and lateral direction and is in agreement with a detailed analysis of the cross correlation of the two sway

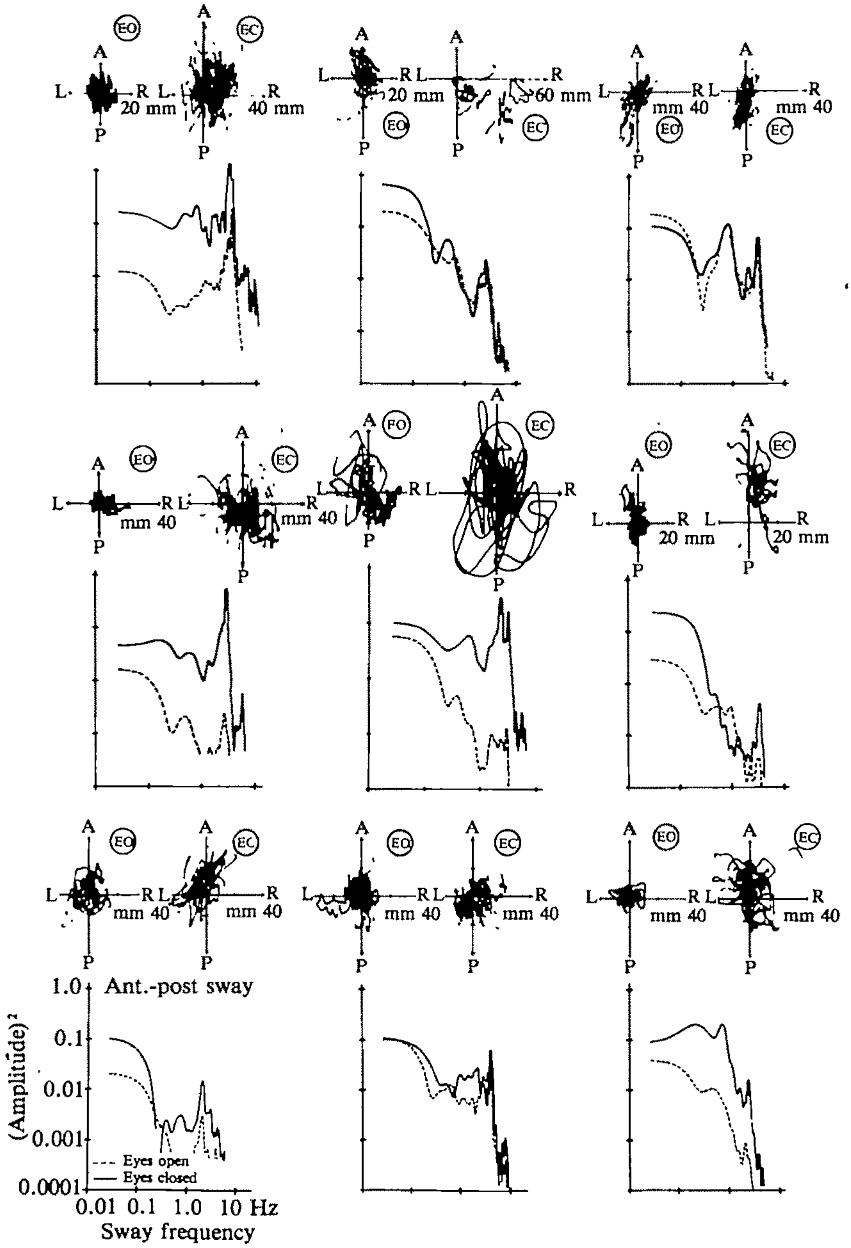

FIG. 3. Body sway data of 9 patients with late cortical cerebellar atrophy recorded with the eyes open (EO) and eyes closed (EC). In each patient x-y plots of the displacement of the centre of force are shown in the upper part and the respective Fourier spectra (eyes open, dotted line; eyes closed, solid line) below.

components in the frequency domain performed by others (Leifer and Meyer, 1975; Litvintsev, 1973). The dotted line and the shaded area in fig. 2 give the average Fourier spectrum of 15 normals and the range for comparison. It may be observed that in the normal Fourier spectrum there is no predominant frequency peak, either in the anterior-posterior or in the lateral direction, and the power is generally less. Both spectra decay smoothly at higher frequencies.

Fig. 3 demonstrates the varying amount of *visual stabilization* for the antero-posterior sway direction in 9 patients. The figure displays the individual sway paths for the eyes closed and eyes open conditions and the corresponding Fourier spectra. Generally, as in normals, the visual stabilization, if present at all, is strongest in the low frequency range.

TABLE 4. BODY SWAY PARAMETERS FOR 28 NORMALS COMPARED WITH 13 PATIENTS WITH LATE CORTICAL CEREBELLAR ATROPHY AND 6 PATIENTS WITH NEOCEREBELLAR TUMOURS (AVERAGES AND STANDARD DEVIATIONS)

	Normals		*Atrophies*		*Tumours*	
Sway parameters	*EO*	*EC*	*EO*	*EC*	*EO*	*EC*
MA	3.44±1.40	4.75±1.65	14.65±5.33	28.48±10.48	5.71±1.79	12.22±7.81
MA (AP)	2.65±1.17	3.52±1.25	10.55±4.67	20.80± 9.84	4.49±1.69	9.67±5.55
MA (lat.)	1.74±0.72	2.51±1.12	7.48±2.79	11.74± 6.93	2.66±1.81	5.04±5.82
SP	0.64±0.28	1.01±0.45	9.97±6.76	20.30±14.78	1.04±0.56	2.84±2.01
SP (AP)	0.50±0.23	0.76±0.34	8.18±6.45	17.47±12.34	0.87±0.48	2.49±1.74
SP (lat.)	0.29−0.16	0.50−0.29	2.26−1.84	6.75− 3.79	0.39−0.28	0.89−1.04

MA = mean amplitude in mm. SP = sway path in m/min. EO = eyes open. EC = eyes closed.

Patients with cerebellar atrophies frequently have severe disturbances of pursuit and optokinetic nystagmus (Dichgans and Jung, 1975; Zee, Yee, Cogan, Robinson and King Engel, 1976). We therefore studied whether, due to the potential loss of opto-motor-interfacing in a more general sense, there was a correlation between the amount of optokinetic nystagmus deficit and the deficiency of visual stabilization of posture. No correlation between the integrated slow phase displacement as a measure of optokinetic nystagmus and the amount of visual stabilization, as expressed by the amplitude ratio of the 3 Hz peak, could be found in the 5 patients studied. We then compared the other sway parameters of this group with those of normals. Table 4 gives the mean amplitude (MA) and the sway path (SP) as well as their anterior-posterior and lateral components in comparison with 28 normals. Differences of both parameters are highly significant ($\alpha = 0.1$ per cent; test according to Scheffé (1959)). The individual patient data fall outside the 2 sigma range of normals with no exception. The parameters chosen therefore are highly reliable for the detection and documentation of pathology. Their specificity with respect to diagnosis is, however, as one would expect, much less than that of the 3/s tremor.

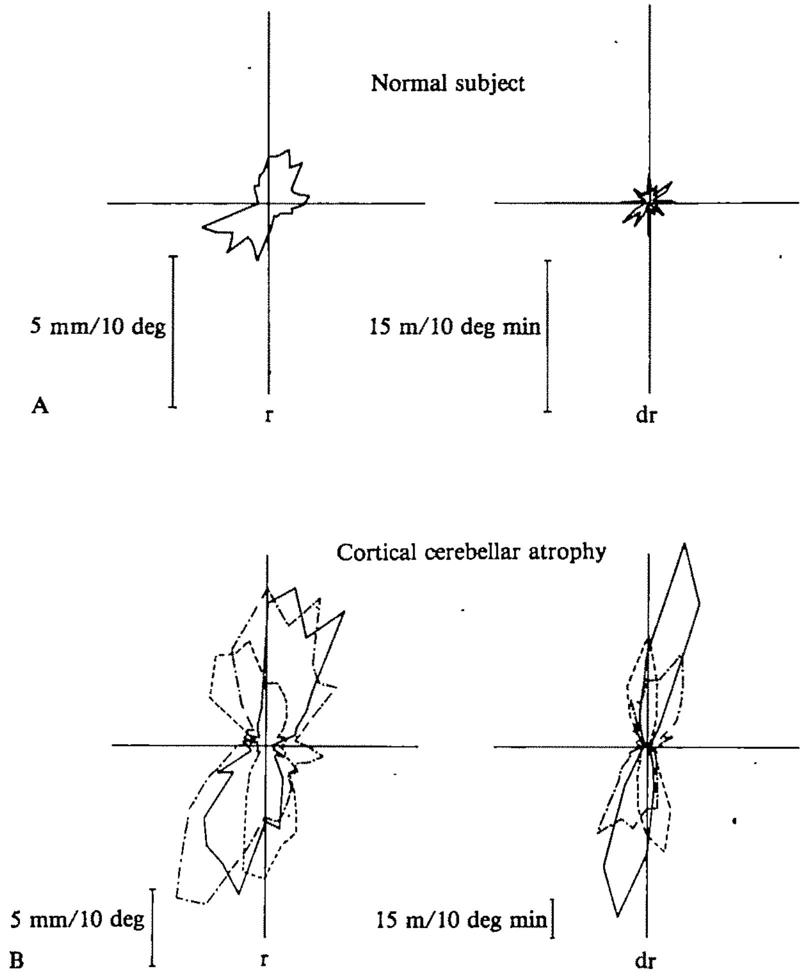

FIG. 4. Sway position (r) and sway direction (dr) histograms of a typical normal (*upper half*) and of 3 patients (*superimposed*) with late cortical cerebellar atrophy (*lower part*) with eyes closed. Note the scale reduction in the lower part; dr-histograms of patients are reduced to $\frac{1}{4}$, the r-histograms to $\frac{1}{2}$.

The sway histograms from 3 patients (1, 3 and 6) and one from a typical normal are shown in fig. 4. The large difference between the position (r-histogram, on the left) and direction histograms (dr-histogram, on the right) from patients and normals can only be appreciated if the different scales are taken into account. The graphs also clearly illustrate the prevalence of antero-posterior instability among the patients. Sway in the strictly lateral direction is particularly small. This causes a notch in the origin of the figure. Similar histograms have not so far been observed in any other disease. They consequently seem characteristic of the disease and useful for diagnosis and documentation.

(b) *Methods for provoking anterior-posterior sway in the early stages.* The disease sometimes develops over a period measured in weeks, in most cases, however, in months, and thenceforth remains rather stable (Victor *et al.*, 1959). At the outset, only a slight ataxia of gait may be noted, without obvious disturbances of upright stance. In 2 of our patients, who were at an early stage of the disease, recordings of spontaneous sway demonstrated no abnormality. Certain manœuvres which suddenly unbalanced the body were, however, able to provoke the antero-posterior tremor. Thus a sagittal body oscillation could be evoked by a rapid active elevation of one arm. Another manœuvre was earlier described by Rademaker and Garcin (1933). They noticed an increase in fore-aft oscillation as a consequence of a rapid push to the trunk. A better controlled stimulus is the rapid tilt of a movable platform used with some of our patients. The postural sway elicited by this manœuvre is exemplified in fig. 5 in comparison with a normal.

Standing on the stable platform with the eyes closed the patient with incipient disease shows only a minimal 3/s oscillation. When the platform is rapidly tilted backwards by 2.15 degrees within 43 ms a long-lasting antero-posterior oscillation of the centre of force is evoked in the patient. With eyes open this oscillation is also present but rapidly decays in amplitude and terminates within three seconds. We were able to re-test the same patient one year later when he presented with the full blown clinical picture and a marked spontaneous 3 Hz tremor. Another method which provokes the oscillation is electrical stimulation of the posterior tibial nerve, described in a separate paper (Mauritz, Dichgans and Schmitt. In preparation).

(c) *Intersegmental response patterns.* It has been stated that patients with the anterior lobe syndrome have exaggerated postural reflexes with positive supporting reactions (Brown, 1949; Victor *et al.*, 1959). The rocking to and fro (Holmes, 1922) may be partially explained by this reflex hyperactivity. Another consequence of this reflex hyperactivity may be the regular intersegmental movements between head, trunk, hips and legs. Though head, hip and centre of force have the same sway frequency, there are characteristic phase differences between these three recordings (fig. 6A). When the triceps suræ contracts the centre of force shifts forward (because of the foot pressure acting on to the platform) and the hip moves backwards. Simultaneously head and trunk move forward, thereby balancing the hip movement (fig. 6B). A similar underdamped balancing oscillation is observed in normals while standing on a narrow rail. These compensating movements belong to the group of fixed intersegmental reaction patterns, the importance of which was first stressed by Bernstein (1967) and Gurfinkel, Kots, Pal'tsev and Feldmann (1971) and which have been recently studied by Nashner (1977).

2. *Neocerebellar Syndrome*

The results obtained from the 6 patients with unilateral hemispheric lesions quite expectedly were diverse. Two patients showed normal stance and in the

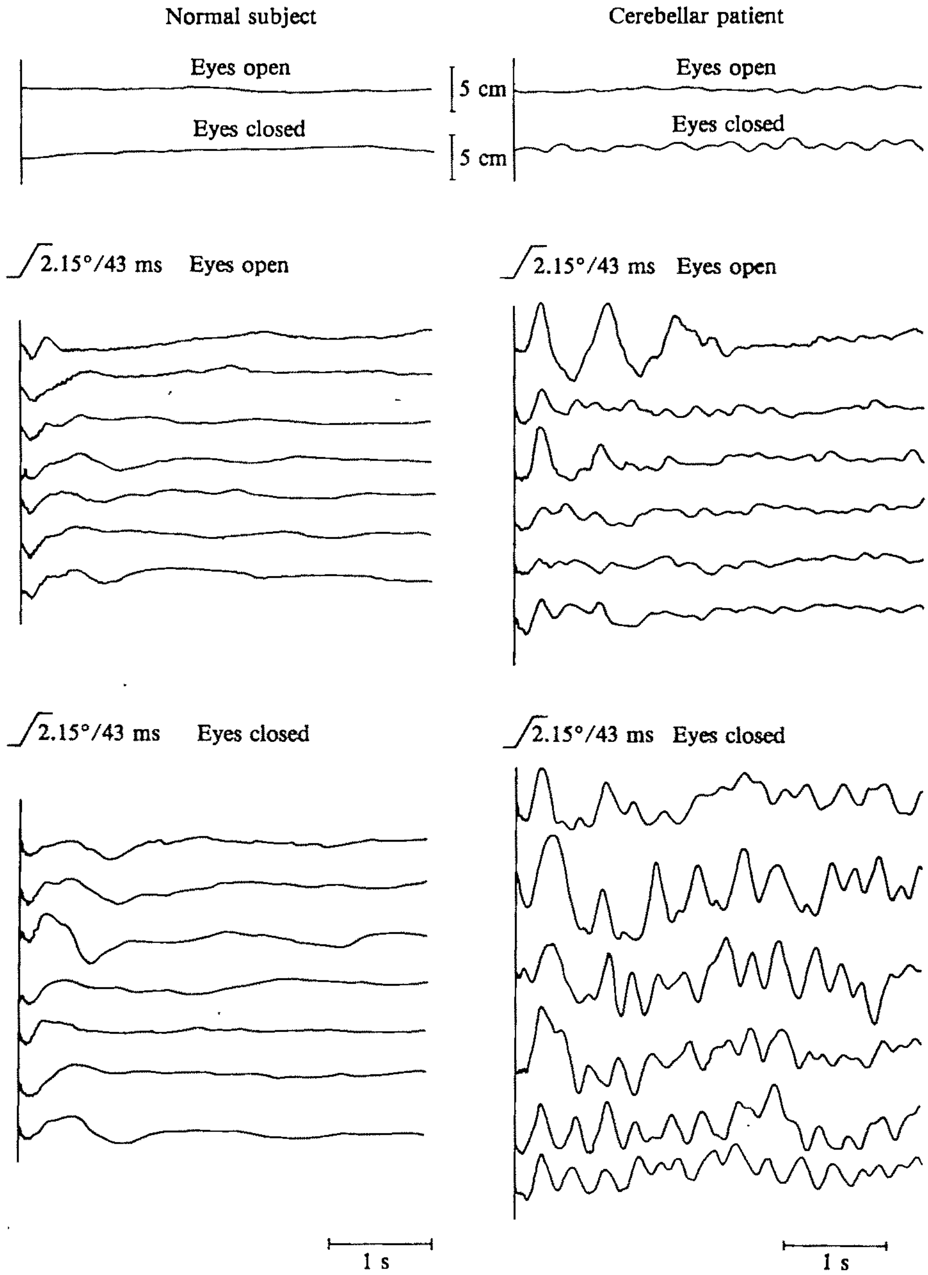

FIG. 5. Effect of a sudden tilt of the measuring platform (backward) upon body sway in a normal and a patient with incipient cerebellar atrophy. *Upper two lines*, control with stable platform. *Below*, several single measurements after rapid tilt (2.15 degrees within 43 ms) with eyes open and eyes closed.

4 remaining ones postural instability was rather slight. Fig. 7 shows original recordings of the lateral and anterior-posterior component, and Fourier power spectra from 3 patients while standing with their eyes open and closed respectively. No 3 Hz tremor and no other characteristic feature could be observed. The spectra are in the normal range or somewhat higher for both directions without a preferred frequency range, indicating that these patients may not readily be distinguished from other postural instabilities of extracerebellar origin by means of their platform recordings.

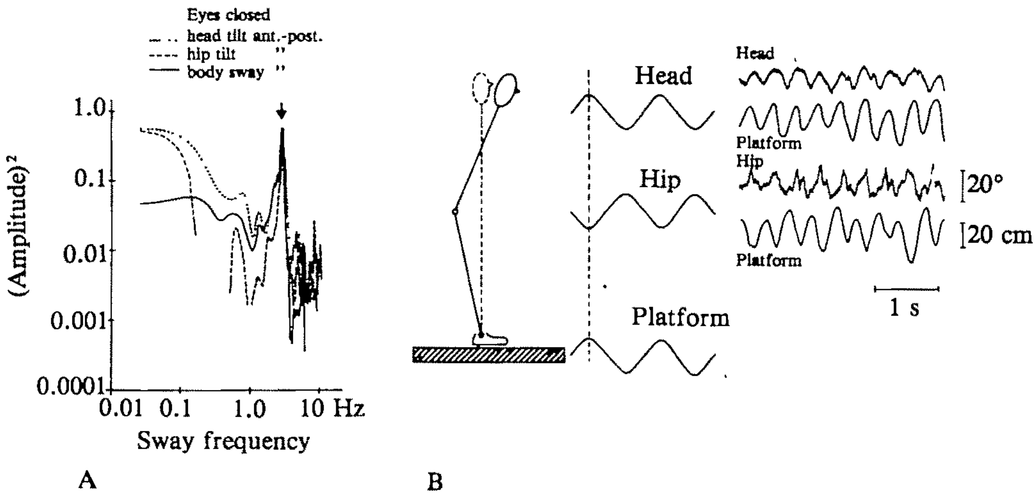

FIG. 6. Movements of different body segments during postural tremor in a patient with cerebellar atrophy. A, Fourier spectra of head and hip tilt movements in the anterior-posterior direction and of the centre of force movements. The arrow marks the 3 Hz peak. B, Original recording of head, hip and platform recordings (*right half*) and schematic illustration of compensatory trunk movements during postural tremor.

The 3 Hz tremor cannot even be provoked by either abruptly displacing the body or electrically stimulating the tibial nerve. The calculated sway parameters MA, SP for this group, although on average above the mean of normals, are within the 2 sigma range (Table 4). Position (r) and direction (dr) histograms of patients within this group show a slightly increased instability for all directions as compared with normals (fig. 8). This is in contrast to the findings of Njiokiktjien (1971) who observed a preponderance of lateral sway. The accentuation of the antero-posterior direction in the dr-histogram is much less than in patients with atrophy (for comparison *see* fig. 4). It is within the range of normality where the antero-posterior sway is up to 50 per cent more than the lateral (Edwards, 1946; Fearing, 1924).

Visual stabilization of posture, as demonstrated by a comparison of postural sway with eyes open and eyes closed, is normal in these patients (figs. 7 and 8).

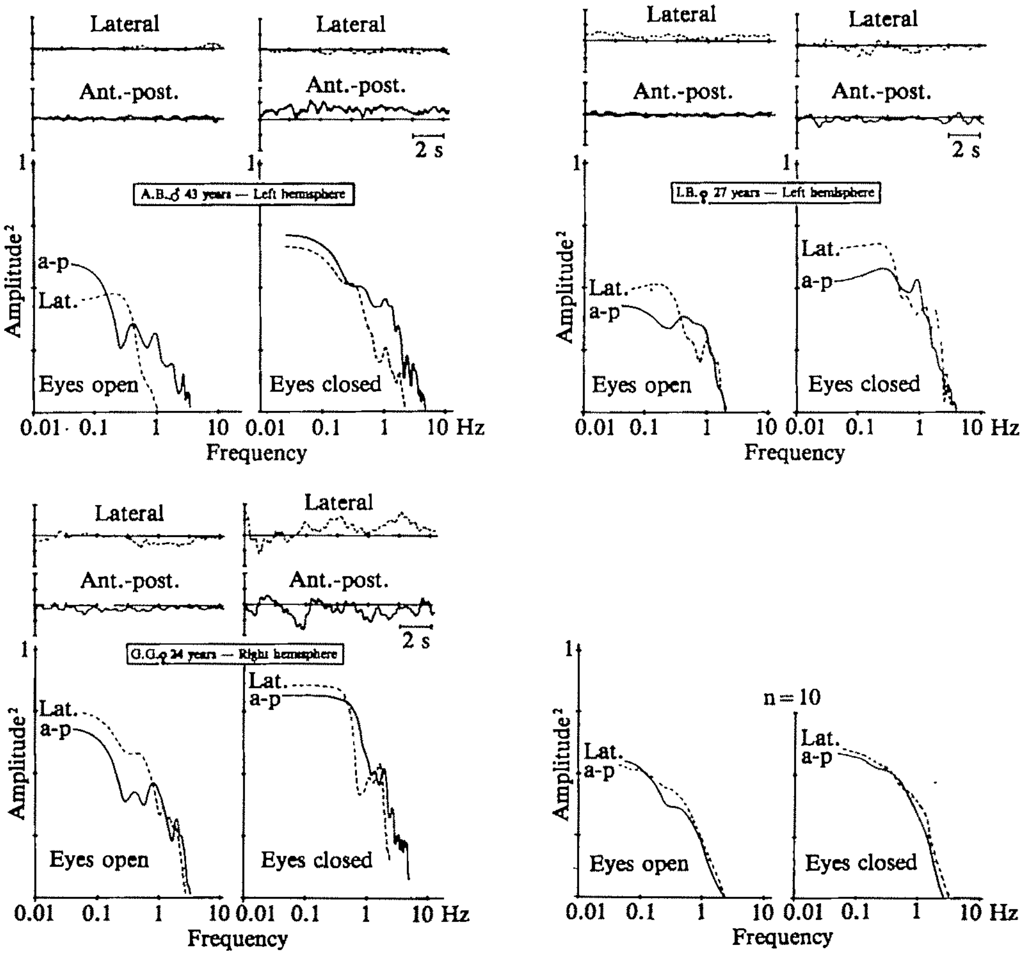

FIG. 7. Fourier spectra of antero-posterior and lateral sway component from 3 patients with a tumour within one cerebellar hemisphere. For comparison, the average spectra from 15 normals (*lower right*). Short segments of the original recordings of the force displacement are shown for both sway directions.

3. *Vestibulo-cerebellar Lesions*

The syndrome of vestibulo-cerebellar lesion (Fulton and Dow, 1937) is most often seen in medulloblastomas which are frequently located in the posterior velum at the base of the nodulus (Ostertag, 1936). Patients—commonly children—show disturbances of balance in stance and walking without appreciable ataxia of the limbs (Bailey, 1933, 1942). The disorders of equilibrium in patients operated on for tumours involving the vestibulo-cerebellum were often so serious that recordings of posture could not be performed, because these patients needed support for upright standing. In two patients, however, it was possible to take recordings for short periods (Table 5). Clinically these patients had severe disturbances of balance with

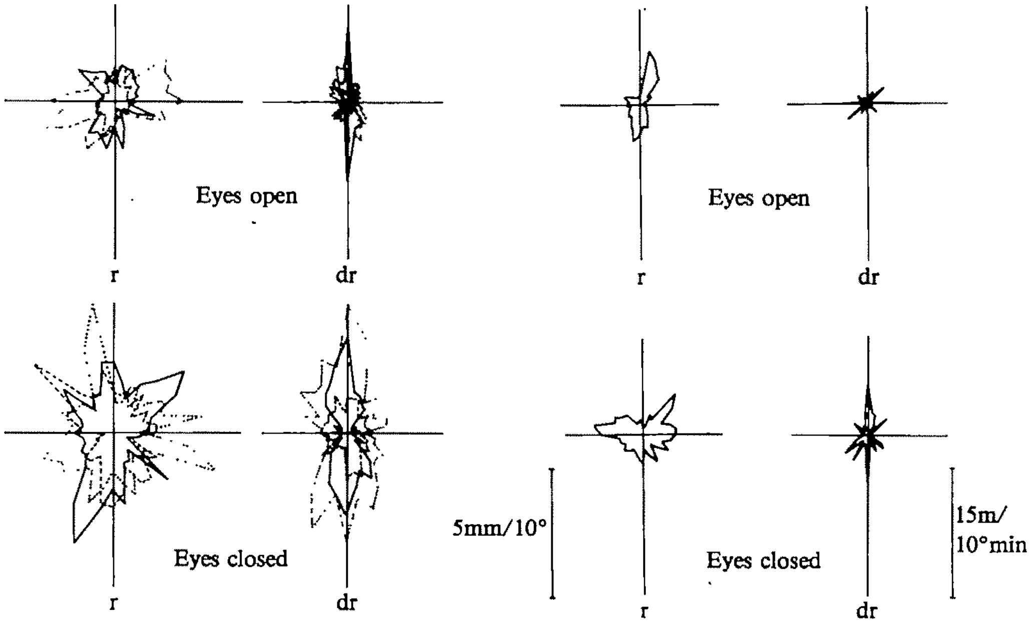

FIG. 8. Sway position (r) and sway direction (dr) histograms from 3 patients with cerebellar hemisphere tumours (superimposed, on the *left*) compared to the equivalent histograms of one typical normal; with eyes open (*upper half*) and eyes closed (*lower half*). — A.B. ♂ left hemisphere. - - - I.B. ♀ left hemisphere. . . . . G.G. ♀ right hemisphere.

slow movements in all directions. Fig. 9, although based on only two patients, suggests that vestibulo-cerebellar lesions cause a prominent low frequency instability of body posture, whereas anterior lobe lesions produce higher frequency components. Again in contrast to the anterior lobe syndrome there is no predominant direction of instability in patients with lesions of the lower vermis.

Fig. 10 plots the orderly relationship between sway path and mean amplitude in normals and all our cerebellar patients. The plot on the one hand illustrates the

TABLE 5. BODY SWAY PARAMETERS FOR 2 PATIENTS WITH MEDULLOBLASTOMA OF THE VESTIBULO-CEREBELLUM (EYES OPEN)

	Patient A	*Patient B*
MA	66.53	51.64
MA (AP)	44.02	29.84
MA (lat.)	39.94	25.43
SP	15.39	10.08
SP (AP)	11.10	6.43
SP (lat.)	8.39	4.25

MA = mean amplitude in mm. SP = sway path in m/min.

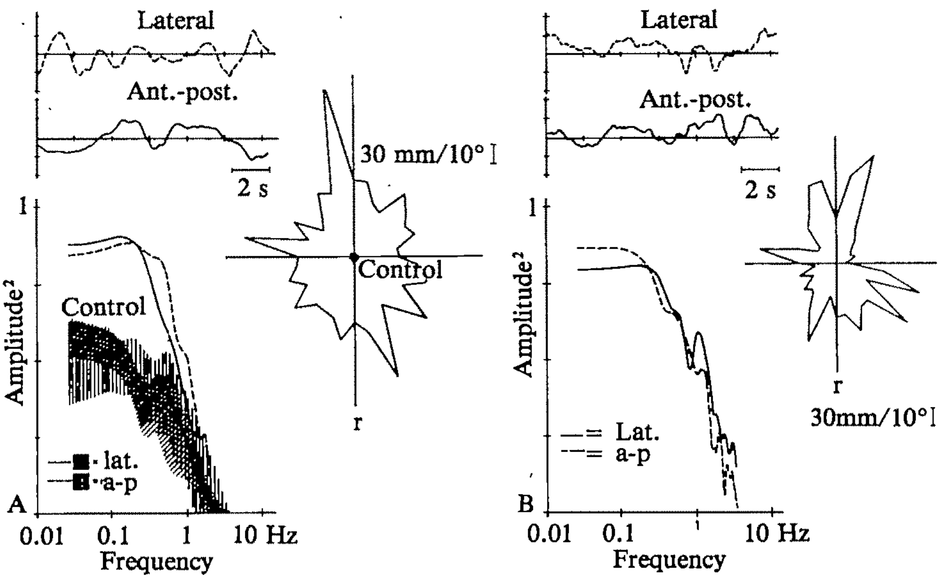

FIG. 9. Body sway data of 2 patients (A and B) with vestibulo-cerebellar lesions. Original recordings of the centre of force, Fourier spectra for lateral (dotted line) and anterior-posterior direction (solid line) and the sway direction histogram are shown and compared to the normal range (shaded areas).

difficulty in differentiating patients with neocerebellar lesions from normals using these parameters. On the other hand, it demonstrates how sway parameters are useful for the discrimination of anterior lobe atrophies and vestibulo-cerebellar lesions from the normal group.

DISCUSSION

Our results agree with classical descriptions of postural instability in paleocerebellar, neocerebellar and archicerebellar syndromes. The quantitative data based on a refined analysis of postural sway may aid differential diagnosis, better documentation and thereby plotting of the time course of the disease. The techniques presented may be useful for future studies of cerebellar function in normals. An increase in tendon reflexes, exaggerated positive supporting reactions and gross disturbances in co-ordination are the consequences of anterior lobe extirpation in cats (Chambers and Sprague, 1955*a*, *b*), primates and man (Brown, 1949; Fulton and Connor, 1939). We also observed the signs of an increased postural reflex gain with anterior lobe diseases, and we interpret the 3 Hz tremor which was earlier described (Dichgans *et al.*, 1976; Mauritz, Dichgans, Hufschmidt and Diener, 1977; Silfverskiöld, 1969, 1977*a*, *b*), as well as augmented intersegmental body reflexes, as its consequence. It may be noted that all but one of our patients with anterior lobe

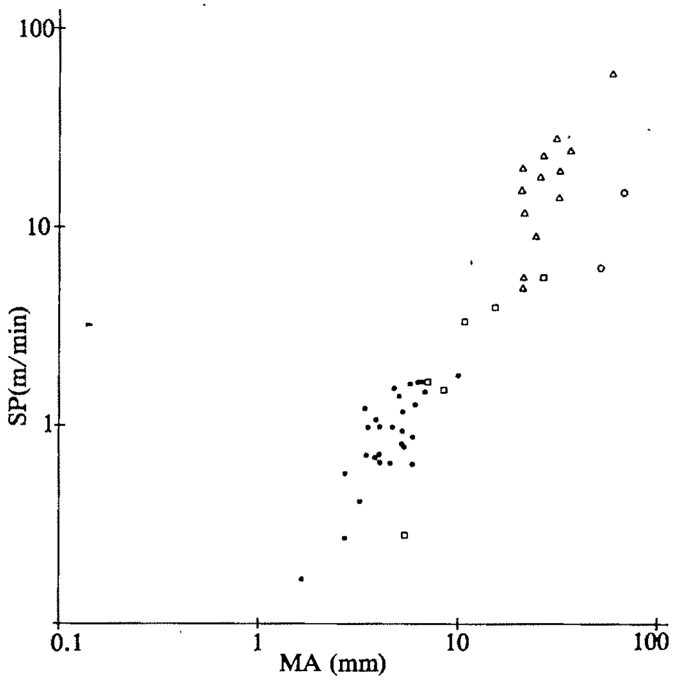

FIG. 10. Relationship between mean amplitude (MA) and length of sway path (SP) for 28 normals (●), 13 patients with late cerebellar atrophy (△), 6 patients with cerebellar hemisphere tumours (□) and 2 patients with vestibulo-cerebellar lesions (○).

atrophy, despite their alcohol misuse, had normal or increased tendon reflexes and, as studied by electromyography, no overt signs of neuropathy. A control group with alcoholic polyneuropathy, but without signs of atrophy of the upper vermis in the computerized tomogram, did not show the 3 Hz anterior-posterior oscillation. Therefore a peripheral origin may be excluded. In incipient cases of cerebellar atrophy the tremor can be elicited by a sudden tilt of the supporting platform or electric shock to the tibial nerve. Normals are rapidly able to damp their reflex response, whereas with anterior lobe diseases a prolonged oscillation of slowly decreasing amplitude and increased long latency discharges are seen (Mauritz *et al.* In preparation). This finding again supports the assumption of an increased reflex gain. The 3 Hz antero-posterior tremor and the disproportionately increased sway parameters in the sagittal plane seem pathognomonic for this syndrome and so far have not been seen with any other localization of cerebellar disease. We assume that the predominance of antero-posterior sway is due to the predominant involvement of the lower limb in postural control, which itself starts increased compensatory intersegmental oscillations between head, trunk, hips and legs. For anatomical reasons the legs have only little motility in the lateral plane. Lateral postural sway consists of postural reactions mainly of the trunk, head and arms. In contrast to the cerebellar control of proprioceptive postural reflexes mainly in the anterior posterior plane, the vestibular system, due to its bilateral organization, is very well suited to control the lateral stability of posture. Correspondingly, patients with uncompensated vestibular lesions show marked lateral sway and eventually fall, as do patients with vestibulo-cerebellar lesions. In these patients it may also be observed that trunk and head are destabilized, even when sitting; this is not seen with pure anterior lobe lesions. The importance of intersegmental response patterns in a multilinked system was stressed by Gurfinkel *et al.* (1971) and Gelfand, Gurfinkel, Tseltlin and Shik (1971), who first suggested preprogrammed fixed patterns during the performance of specific tasks, and also demonstrated one case with a tumour in the posterior fossa in which these intersegmental responses were disturbed. The fact that patients with cortical cerebellar atrophy rarely fall, despite their instability (Garcin, 1969), may be due to their intact and even exaggerated intersegmental responses.

The ability to stabilize posture by vision is preserved in some cases of anterior lobe atrophy but is totally absent in others. A clear correlation between the severity of postural ataxia and the amount of visual stabilization could not be found. This may be due to the different projection of visual afferences (in lobuli V–VII and the flocculus) as opposed to the spinocerebellar projections in the anterior lobe. In some cases the areas which receive visual input may be involved in addition and therefore may cause a lack of visual stabilization; in others these areas are presumably spared. The poor correlation between the amount of visual stabilization and the quality of optokinetic nystagmus and smooth pursuit, suggest different sites of visuomotor interfacing for posture and eye movements within the cerebellum. In any case, it is not true that Romberg's sign is invariably negative in cerebellar patients (Dow and Moruzzi, 1958).

The neocerebellar syndrome, in contrast to the anterior lobe ataxia, mostly causes no or only slight postural instability, which even with careful analysis shows no characteristic feature so far. Ablation experiments in primates, although resulting in hypotonia and ataxia of the limbs, did not cause severe postural ataxia. The preoccupation of the neocerebellum with reaching, grasping, and other goal-directed movements of the limbs, but not with posture, is also indicated by experiments with reversible cooling (Meyer-Lohmann, Conrad, Matsunamin and Brooks, 1975; Thach, 1970, 1975; Conrad and Brooks, 1975).

The third group of patients, with vestibulo-cerebellar lesions of the posterior vermis and the flocculo-nodular lobe, exhibits the severest postural ataxia. Most patients show a heavy trunk ataxia even when sitting (Bailey and Cushing, 1925). The results of the admittedly small sample of two patients agree with clinical observations and therefore may probably be taken as representative. The largest deviations of the centre of gravity within this group are in the low frequency range and show no preferential direction. It seems as if the system, having lost its set value, drifts and shows poor control activities; whereas, with anterior lobe lesions, the correct position seems to be known to the system, but the control loops seem to oscillate because of increased gain and transmission delay. Though our results are far from being conclusive with respect to an understanding of the role of the cerebellum in posture, we are beginning to use the results of this analysis for the clinical classification of cerebellar lesions and have been increasingly successful, particularly in early cases of anterior lobe atrophy and vestibulo-cerebellar lesions.

SUMMARY

(1) Methods have been developed to measure, analyse and document postural sway. The main parameters studied were: average sway amplitude; length of the sway path per unit time; sway direction and sway position histograms; and the frequency spectra of the antero-posterior and lateral sway components.

(2) Postural ataxia was quantitatively studied in three groups of patients with cerebellar lesions: (*a*) late atrophy of the anterior lobe, (*b*) tumours of the cerebellar hemisphere and (*c*) tumours within the vestibulo-cerebellum. Characteristic differences were found.

(3) Patients with anterior lobe lesions show a specific 3 Hz postural tremor in the antero-posterior direction. The tremor can be evoked by sudden destabilization in incipient cases. Less characteristic and smaller in amplitude is a mainly lateral sway component with an average frequency of 0.5 Hz. This is also seen in cases with spinal ataxia. Visual stabilization of posture is frequently preserved. Its amount does not correlate with general instability of posture. Tremor and characteristically exaggerated intersegmental responses between head, trunk, hips and legs are interpreted as the consequence of hyper-excitability of postural reflexes in these patients.

(4) Patients with lesions of the hemispheres show only slight postural instability without directional preference. Their sway parameters with eyes open are within the 2 sigma range of normals and there is no significant difference from normals in these parameters even when the eyes are closed. Therefore these patients cannot be distinguished from normals by means of their platform recordings.

(5) Two patients with posterior vermal and flocculo-nodular lesions were very unstable without preferred axis or frequency of instability. In contrast to the anterior lobe group the instability was characterized by the absence of intersegmental movements.

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REFERENCES

ALLUM, J. H. J., DIETZ, V. and FREUND, H.-J. (1978) Neuronal mechanisms underlying physiological tremor. *Journal of Neurophysiology*, **41**, 557–571.

BAILEY, P. (1933) *Intracranial Tumors.* Springfield: Charles C. Thomas, Chapter 11.

—— (1942) Reflections aroused by an unusual tumor of the cerebellum. *Journal of the Mount Sinai Hospital*, **9**, 299–310.

—— and CUSHING, H. (1925) Medulloblastoma cerebelli: a common type of midcerebellar glioma of childhood. *Archives of Neurology and Psychiatry, Chicago*, **14**, 192–223.

BERNSTEIN, N. (1967) *Coordination and Regulation of Movements.* New York: Pergamon Press, Part I, pp. 66–100.

BRODAL, A. (1969) *Neurological Anatomy.* London: Oxford University Press, Chapter 5.

—— (1972) Cerebrocerebellar pathways; anatomical data and some functional implications. *Acta Neurologica Scandinavica*, **48**, Suppl. 51, 153–195.

BROWN, J. R. (1949) Localizing cerebellar syndromes. *Journal of the American Medical Accociation*, **141**, 518–521.

CHAMBERS, W. W. and SPRAGUE, J. M. (1955*a*) Functional localization in the cerebellum. I. Organization in longitudinal corticonuclear zones and their contribution to the control of posture both extrapyramidal and pyramidal. *Journal of Comparative Neurology*, **103**, 105–130.

—— —— (1955*b*) Functional localization in the cerebellum. II. Somatotopic organization in cortex and nuclei. *Archives of Neurology and Psychiatry, Chicago*, **74**, 653–680.

CONRAD, B. and BROOKS, V. B. (1975) Cerebellare Bewegungsstörungen im Tierversuch. Vergleich rascher Alternativbewegungen und langsamerer Zielbewegungenwährend reversibler Dentatusausschaltungen. *Journal of Neurology*, **209**, 165–179.

DICHGANS, J. and JUNG, R. (1975) Oculomotor abnormalities due to cerebellar lesions. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications.* Edited by G. Lennerstrand and P. Bach-y-Rita. Oxford: Pergamon Press.

—— MAURITZ, K. H., ALLUM, J. H. J. and BRANDT, Th. (1976) Postural sway in normals and ataxic patients: Analysis of the stabilizing and destabilizing effects of vision. *Agressologie*, **17C**, 15–24.

—— REUTERN, G. M. VON and RÖMMELT, U. (1978) Impaired suppression of vestibular nystagmus by fixation in cerebellar and noncerebellar patients. *Archiv für Psychiatrie und Nervenkrankheiten*, **226**, 183–199.

DOW, R. S. (1969) Cerebellar syndromes including vermis and hemispheric syndromes. In: *Handbook of Clinical Neurology.* Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, Vol. 2 pp. 392–431.

—— and MORUZZI, G. (1958) *The Physiology and Pathology of the Cerebellum.* Minneapolis: The University of Minnesota Press, pp. 378–398.

EDWARDS, A. S. (1946) Body sway and vision. *Journal of Experimental Psychology*, **36**, 526–535.

FEARING, F. S. (1924) An experimental study of the effects of practice upon amount and direction of sway. *Journal of Comparative Psychology*, **4**, 163–188.

FIELDS, W. S. and WILLIS, W. D. Jr. (1970) *The Cerebellum in Health and Disease.* London: Adam Hilger.

FULTON, J. F. and CONNOR, G. (1939) The physiological basis of three major cerebellar syndroms. *Transactions of American Neurology* **65**, 53-57.

—— and DOW, R. S. (1937) The cerebellum: A summary of functional localization. *Yale Journal of Biology and Medicine*, **10**, 89-119.

GARCIN, R. (1969) The ataxias. In: *Handbook of Clinical Neurology.* Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, Vol. 1, pp. 309-355.

GELFAND, J. M., GURFINKEL, V. S., TSELTLIN, M. L. and SHIK, M. L. (1971) Problems in the analysis of movements. In: *Models of the Structural-Functional Organization of Certain Biological Systems.* Edited by V. S. Gurfinkel, S. V. Fomin and M. L. Tsetlin. London: MIT Press, pp. 330-345.

GRANT, G. (1962*a*) Spinal course and somatotopically localized termination of the spinocerebellar tracts. An experimental study in the cat. *Acta Physiologica Scandinavica*, **56**, Suppl. 193, 1-45.

—— (1962*b*) Projection of the external cuneate nucleus onto the cererebellum in the cat: An experimental study using silver methods. *Experimental Neurology*, **5**, 179-195.

GURFINKEL, E. V. (1973) Physical foundations of the stabilography. *Agressologie*, **14G**, 9-14.

—— KOTS, Ya. M., PAL'TSEV, Y. J. and FELDMANN, A. G. (1971) The compensation of respiratory disturbances of the erect posture of man as an example of the organization of inter-articular interaction. In: *Models of the Structural-Functional Organization of Certain Biological Systems.* Edited by E. V. Gurfinkel, S. V. Fomin and M. L. Tsetlin. London: MIT Press, pp. 382-395.

HOLMES, G. (1922) The Croonian Lectures on the clinical symptoms of cerebellar disease and their interpretation. *Lancet*, **100 (1)**, 1177-1182, 1231-1237; **100 (2)** 59-65.

HUFSCHMIDT, A. (1977) Die quantitative Beschreibung der spontanen Körperschwankungen im Stehen: Meßmethode, Meßgrößen, experimentell-physiologische und klinische Anwendung. Dissertation, Universität Freiburg.

KONONOVA, E. (1926) Die Lokalisation der Funktion des Kleinhirns. *Zentralblatt für die Gesamte Neurologie und Psychiatrie*, **44**, 597.

LEIFER, L. J. and MEYER, M. (1975) Postural mode description by correlation and transfer function measurement. *Proceedings of 1975 IEEE Systems, Man and Cybernetics*, San Francisco.

LITVINTSEV, A. J. (1973) Mechanisms of Man's vertical posture control. *Agressologie*, **14B**, 17-21.

MARIE, P., FOIX, C. and ALAJOUANINE, T. (1922) De l'atrophie cérébelleuse tardive à prédominance corticale. *Revue Neurologique*, **38**, 849-885, 1082-1111.

MAURITZ, K. H., DICHGANS, J., ALLUM, J. H. J. and BRANDT, Th. (1975) Stabilization and destabilization of posture by vision. *Experimental Brain Research.* **23**, Supplement 138, Abstract No. 272.

—— —— HUFSCHMIDT, A. and DIENER, H.-C. (1977) Quantitative measurements of cerebellar ataxias. *IVth International Symposium of Posturography*, Sofia. Abstract 35.

—— —— SCHMITT, C. (1979) Postural tremor in cerebellar atrophy of the anterior lobe may be caused by enhanced and delayed long latency reflexes. In preparation.

MEYER-LOHMANN, J., CONRAD, B., MATSUNAMIN, K. and BROOKS, V. B. (1975) Effects of dentate cooling on precentral unit activity, following torque pulse injections into elbow movements. *Brain Research, Amsterdam*, **94**, 237–251.

NASHNER, L. M. (1977) Fixed patterns of rapid postural responses among leg muscles during stance. *Experimental Brain Research*, **30**, 13–24.

NJIOKIKTJIEN, C. (1971) Statokinesimetrische registratie van het houldingsevenwicht. Thesis, Vrije Universiteit, Amsterdam.

—— and VAN PARYS, J. A. P. (1976) Romberg's sign expressed in a quotient. II. Pathology. *Agressologie*, **17D**, 19–24.

OSTERTAG, B. (1936) *Einteilung und Characteristik der Hirngewächse.* Jena: G. Fischer, pp. 41–48.

RADEMAKER, G. G. J. and GARCIN, R. (1933) L'épreuve d'adaptation statique. Suite à l'étude de quelques réactions des extrémités d'origine labyrinthique. *Revue Neurologique*, **2**, 566–579.

SCHEFFÉ, H. (1959) *The Analysis of Variance.* New York: John Wiley, Chapter 6.

SILFVERSKIÖLD, B. P. (1969) Romberg's test in the cerebellar syndrome occurring in chronic alcoholism. *Acta Neurologica Scandinavica*, **45**, 292–302.

—— (1977*a*) Cortical cerebellar degeneration associated with a specific disorder of standing and locomotion. *Acta Neurologica Scandinavica*, **55**, 257–272.

—— (1977*b*) A 3 c/sec leg tremor in a 'cerebellar' syndrome. *Acta Neurologica Scandinavica*, **55**, 385–393.

THACH, W. T. (1970) Discharge of cerebellar neurones related to two maintained postures and two prompt movements. I. Nuclear cell output. *Journal of Neurophysiology*, **33**, 527–536.

—— (1975) Tuning of activity in cerebellar dentate nucleus and cerebellar motor cortex during prompt volitional movements. *Brain Research, Amsterdam*, **88**, 233–241.

VICTOR, M., ADAMS, R. D. and MANCALL, E. L. (1959) A restricted form of cerebellar cortical degeneration occurring in alcoholic patients. *Archives of Neurology, Chicago*, **1**, 579–688.

—— and FERRENDELLI, J. A. (1970) The nutritional and metabolic diseases of the cerebellum. Clinical and pathological aspects. In: *The Cerebellum in Health and Disease.* Edited by W. S. Fields and W. D. Willis. London: Adam Hilger, pp. 412–419.

ZEE, D. S., YEE, R. D., COGAN, D. G., ROBINSON, D. A. and KING ENGEL, W. (1976) Ocular motor abnormalities in hereditary cerebellar ataxia. *Brain* **99**, 207–234.

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ALTERED CHROMATIN CONFORMATION IN ALZHEIMER'S DISEASE

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INTRODUCTION

THERE are indications that altered protein synthesis is a major disorder in senile and presenile dementia of the Alzheimer type. The reduced brain weight and size of cortical dendrites (Scheibel and Tomiyasu, 1978) and the biochemical studies of Suzuki, Katzman and Korey (1965) on biopsy material of Alzheimer affected brain indicated a selective decrease in the ratio of proteins to lipids and implicated reduced protein synthesis. Nucleolar size, a useful index of protein synthesis, is decreased in Alzheimer's disease (Dayan and Ball, 1973; Mann and Sinclair, 1978). Suzuki *et al.* (1965) found no difference in the incorporation of labelled amino acid into protein by microsomes prepared from two Alzheimer brain biopsies compared to control microsomes, an observation which favours a deficit in processes involving transcription rather than translation. Hyden (1962) and Ringborg (1966) reported a decrease with age in RNA content of isolated neurons. A decrease in RNA to DNA ratio was measured in cerebral cortex of brains with senile dementia by Bowen, Smith, White, Goodhardt, Spillane, Flack, Davison, Carrasco and Gedye (1977*a*, *b*) and these workers reported a decrease in the percentage of total protein accounted for by microsomal proteins (Bowen, Smith and Davison, 1973). Decreased RNA content has also been observed by histological techniques in senile dementia (Mann and Sinclair, 1978). These observations favour an alteration in RNA processing. Since chromatin is the site of RNA production, the present study was undertaken to test the hypothesis that alterations in chromatin conformation might be associated with both decreased cytoplasmic RNA and depressed protein synthesis.

METHODS

Specimens

Human brains. Human brains were bisected in the sagittal plane and one half fixed in formalin and the other frozen at −90° C. On the basis of clinical history and extensive histological examination the following groups were made. Control Group 1 was composed of 12 brains of patients aged 2 to 69 years. The brains were completely free of senile plaques and neurofibrillary degeneration and the patients had no history of dementia. Control Group 1 also contained Control Group 2 consisting of

5 brains from patients aged 53 to 69 years which was extracted for purposes of age matching. An Alzheimer Group contained 12 brains ranging in age from 53 to 95 years. These brains had widespread senile plaques and tangles and were obtained from patients with a history consistent with the diagnosis of Alzheimer's disease. An additional 5 brains were obtained from patients who died following prolonged dialysis for renal failure. Two of these patients had a clinical history of profound dementia and three cases were moderately demented. A final group of 5 brains, designated the Intermediate Group, ranged in age from 62 to 88 years and were found to have some neurofibrillary degeneration and senile plaques; however the clinical history or additional neuropathological findings precluded the diagnosis of Alzheimer's disease.

Biochemical Analyses

Isolation of nuclei. Nuclei from both neurons and glia of cerebral cortex were isolated in sucrose solutions using methods modified from Yasmineh and Yunis (1970). All steps were carried out at 4° C. 10 to 50 g of cerebral cortical grey matter were washed three times in 30 ml of 0.9 per cent NaCl (W/V) and homogenized in 10 volumes of 0.32 M sucrose-1.5 mM $CaCl_2$ using a Potter-Elvehjem homogenizer. The homogenate was filtered through 153 μm nylon bolting, centrifuged at 4000 × g (R_{av}) for 10 min and the pellet washed three times with 0.32 M sucrose-1.5 mM $CaCl_2$. The washed nuclear pellet was then resuspended in 1.62 M sucrose-1.5 mM $CaCl_2$ and centrifuged at 8000 × g for 60 min. The resulting pellet was suspended in 2.2 M sucrose-1.5 mM $CaCl_2$ and centrifuged at 30 000 × g for 50 min. Removal of remaining cytoplasmic tags was achieved by washing four times with 10 ml aliquots of 0.1 M Tris-1.5 mM $CaCl_2$ at pH 7.1 and centrifugation for 5 min at 4000 × g. Finally the pellet was suspended in 6 ml of 0.25 M sucrose and 2 ml of this was removed for the determination of protein and DNA. After each isolation, nuclei were viewed by phase contrast microscopy or stained with 0.1 per cent (W/V) toluidine blue and examined for cytoplasmic remnants. Nuclei were also prepared for electron microscopy by standard methods.

Isolation of chromatin fractions. Nuclei were broken by sonication for three thirty-second intervals employing 50 per cent maximum power from a Branson Cell Disruptor 185 with microtip. Microscopy confirmed complete disruption of nuclei. From the resulting suspension three fractions of chromatin were obtained: a heavy fraction of heterochromatin which was sedimented by centrifugation at 4000 × g for 20 min, an intermediate euchromatin fraction sedimented by centrifugation at 100 000 × g for 1 h and a supernatant light euchromatin fraction. The pellets of hetero- and intermediate chromatin were resuspended in 3 ml of 0.25 M sucrose; 0.5 ml aliquots of the chromatin fractions were removed for aluminium, DNA and protein determination.

Isolation of neuronal and glial nuclei. Neuronal and glial enriched nuclear fractions were separated by the method of Fleischer-Lambropoulos and Reinsch (1971). The nuclei were suspended in 0.25 M sucrose and layered on the discontinuous gradients. After centrifuging the neuronal nuclei were collected from the 2.4 to 2.5 M interface and the glial nuclei from the 2.5 to 2.6 M interface. The fractions were washed twice with 0.25 M sucrose and examined by light microscopy. From representative preparations histogram distributions of nuclear diameters were obtained and used as an index of separation. The enriched nuclear fractions were sonicated and complete disruption confirmed by light microscopy. The chromatin fractions were separated by centrifugation.

Transcription of chromatin. Hetero- and euchromatin were transcribed with *Escherichia coli* RNA polymerase (Sigma) using a modification of the method of Cedar and Felsenfeld (1972). The reaction mixture was composed of the following: 1.5 μg DNA in 200 μl of 10 mM Tris-HCl (pH 7.9), lmM $MnCl_2$, 200 μl of ATP and GTP in Tris-HCl, $CaCl_2$ and 0.02 mM (H^3) UTP (25.2 C_i/m mol). The reaction was started by adding 50 μl *E. coli* RNA-polymerase and the mixture incubated at 37° C for 15 min. To prevent further initiation, 0.16 ml of 1.6 M $(NH_4)_2SO_4$ was added. The elongation process was then started by the addition of CTP (final concentration 0.063 mM) and $MgCl_2$ (final concentration 5 mM) and incubation at 37° C for 30 min. Subsequently, the reaction mixture was placed on ice for 30 min.

Five 100 μl aliquots were spotted on DEAE impregnated filter paper (Altman and Lerman, 1970) and heat dried between applications. To increase counting efficiency the DEAE filter papers were not dried after the final application but blotted and placed in the scintillation fluid. The samples were counted in a Unilux II model 6853 B-scintillation counter. Chromatin blanks containing no enzyme were routinely run and the blank values subtracted from the samples.

Chain length distribution of RNA produced *in vitro* from the euchromatin fraction was measured using the method of Cedar and Felsenfeld (1972). Wheat embryo RNA served as a marker to standardize the gradients.

Analytical Methods

DNA standards (Sigma Lot 26C-9540 from calf thymus containing less than 50 μg protein/g DNA) were prepared in 0.25 M sucrose and diluted 1:1 with 0.1 per cent sodium lauryl sulphate. Samples for DNA determination were prepared in a similar manner and read at 260 nm on a Gilford Model 2400 spectrophotometer according to the method of Levy, Levy, Rosenberg and Simpson (1973). Isolated brain nuclei contain 8 to 15 per cent RNA which contributes to the optical density at 260 nm. Protein was measured by the method of Lowry, Rosenbrough, Farr and Randall (1951), using bovine serum albumin as the standard.

Statistical Analysis

The significance of differences between groups of data was analysed by Student's t-test.

RESULTS

A. Nuclear Pellet

Both light and electron microscopic examination of the nuclear pellets revealed that nuclei were largely free of cytoplasmic tags and the infrastructure of the nuclei remained intact (fig. 1).

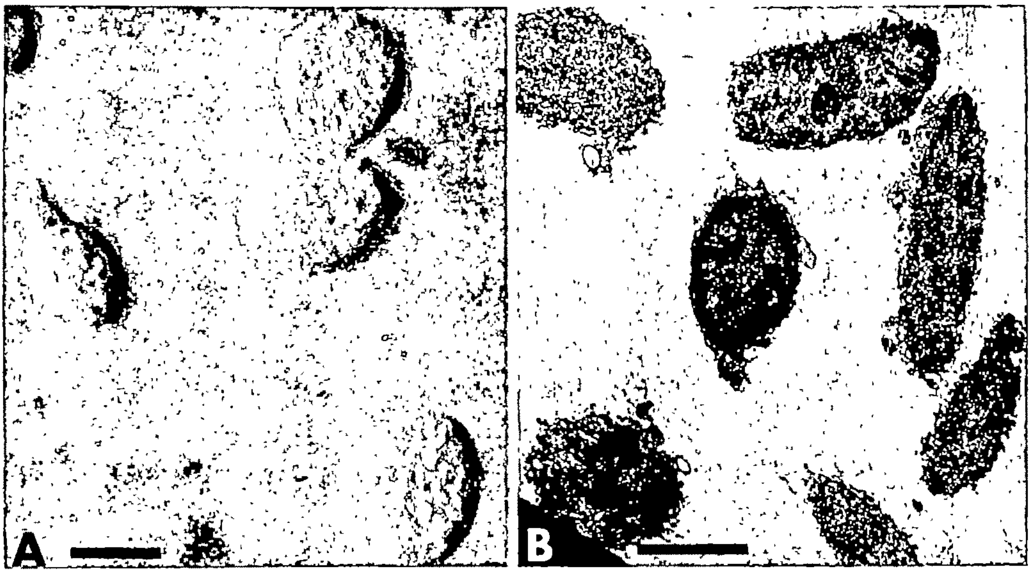

FIG. 1. Nuclear fraction upon which DNA, protein and aluminium were determined: A, interference contrast photomicrography; B, electron micrograph. Bars = 5 μm.

The average diameter of nuclei in the homogenate of cerebral cortex after the first step in the isolation procedure was 7.3 ± 3.2 SD μm (n = 340). After the final step in the isolation the average diameter was 6.7 ± 3.2 SD μm (n = 346) indicating that the procedures did not alter the population of cerebral cells from which the chromatin was derived. These values are similar to the average nuclear diameter of 6.0 μm (n = 454) measured in formalin-fixed, paraffin-embedded, hæmatoxylin and eosin stained tissue from human temporal lobe taken from contralateral hemispheres.

B. Chromatin Conformation in Whole Cerebral Cortex

In 21 nuclear preparations from 12 control brains of patients aged 2 to 69 years, the percentage of DNA in the euchromatin state (intermediate plus light fraction) was 75.2 ± 5.5 SD per cent (Table 1, Control Group 1). As shown in table 2, the distribution of DNA in chromatin fractions from control brain was closely similar for nuclear preparations taken from different cortical regions in the same brain.

Subdividing the euchromatin into fractions, the percentage of DNA in the intermediate fraction was 53.6 ± 8.3 SD per cent of the total and in the light fraction was 21.3 ± 9.7 SD per cent, a ratio of approximately 2:1.

In 25 preparations from 12 brains with advanced Alzheimer's disease, the distribution of DNA in the euchromatin form varied between 78 and 26 per cent with an average value of 55.6 ± 16.8 SD per cent (Table 1, fig. 2). Compared to the control brains, the euchromatin content varied widely in different regions of cortex from the same brain (*see* Table 2). As in the control brains, intermediate euchromatin contained about twice as much of the total DNA as did the light euchromatin fraction (Alzheimer intermediate euchromatin 38.5 ± 13.2 SD per cent and light euchromatin 17.4 ± 6.4 SD per cent to total DNA).

The observed increase in the proportion of heterochromatin in advanced Alzheimer's disease could be related to a number of non-specific factors including age, the altered physiological state associated with dementia, gliosis, the duration of the terminal illness and post-mortem events including the interval between death and tissue freezing and the length of storage. To evaluate the possible contribution of these factors to the conformation of chromatin, the following studies were performed.

TABLE 1. AVERAGE EUCHROMATIN CONTENT OF MIXED NEOCORTICAL NUCLEI, EXPRESSED AS PERCENTAGE OF TOTAL DNA

Group	*Age range*	*No. of brains*	*No. of preparations*	*Euchromatin* $\bar{X}$ *SD*
Control 1	2–69	12	21	75.2 ± 5.5
Control 2	53–69	5	7	74.6 ± 3.5
Alzheimer	53–95	12	25	55.6 ± 16.8
Presenile Alzheimer	53–69	6	11	53.2 ± 19.3
Dialysis dementia	38–69	5	9	74.5 ± 5.5
Intermediate	62–88	5	10	79.6 ± 5.0

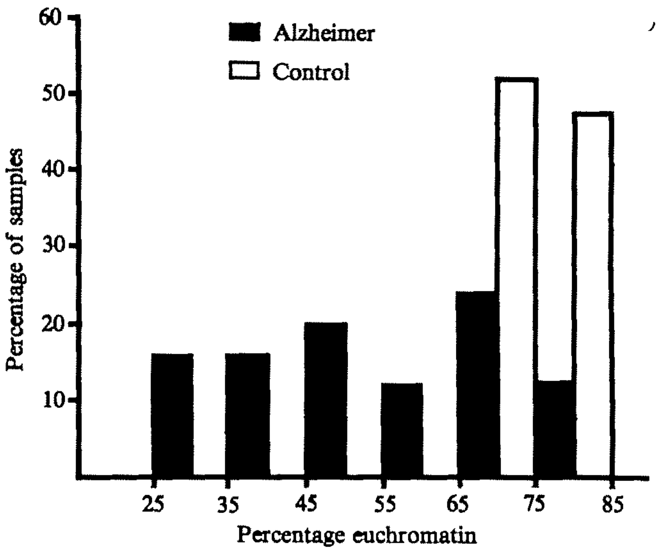

FIG. 2. Histogram of distribution of euchromatin in Control Group 1 and the Alzheimer Group.

To examine the effect of age, the average value for euchromatin in 11 preparations from 6 presenile Alzheimer brains ranging in age at death from 53 to 69 years (mean = 65) was measured and found to be 53.2±19.3 SD per cent (Table 1 presenile Alzheimer Group). In an age-matched group of 5 Control brains between 53 and 69 years (mean = 59), the average euchromatin content was 74.6±3.5 SD per cent (Table 1, Control Group 2). While the age differences between the groups was not significant, the difference in euchromatin content was significant at the $P < 0.01$ level.

The altered physiological state of the cortex associated with dementia together with the long terminal illness might also contribute to heterochromatization. In 2 cases of profound dementia and 3 cases of moderate dementia of more than six months' duration associated with chronic renal failure and dialysis and ranging in age from 38 to 69 years (mean = 56), the average euchromatin content was 74.5±5.5 SD per cent (n = 9), a value not significantly different from the Control

TABLE 2. EUCHROMATIN DISTRIBUTION FOR SPECIFIC BRAIN REGIONS (% TOTAL DNA), FOR 2 CONTROL AND 2 ALZHEIMER AFFECTED BRAINS

Neocortical location	*Control*		*Alzheimer*	
	1	2	1	2
Medial temporal	73.2	—	42.7	60.5
Frontal	74.6	73.4	25.8	52.2
Parietal	76.0	79.4	—	37.1
Occipital	72.1	79.5	30.6	—
$\bar{X}$, SD	74.0±1.7	77.4±3.5	33.0±8.7	49.9±11.9

brains. As in the Alzheimer cases, bronchopneumonia was a terminal event. Therefore heterochromatization does not appear to accompany the dementia associated with dialysis encephalopathy or with bronchopneumonia as a terminal event.

The increase in heterochromatin does not appear to occur with advanced age or minimal pathological changes of Alzheimer's disease. The Intermediate Group (Table 1), was composed of 5 brains. In one case, aged 71 years, a two-year history of dementia was associated with renal failure and hypertension. The brain weighed 1200 g and contained rare micro-infarcts and very occasional plaques and tangles. An experienced neuropathologist (N.B.R.), was unable to assign a specific histopathological diagnosis. In a second case, aged 88 years, a long history of profound dementia was associated with a brain weight of 879 g and multiple small infarcts together with rare plaques and tangles. A diagnosis of multi-infarct dementia was made. A third case, aged 75 years, was said to be intellectually intact but had scattered plaques and tangles. None of these cases exhibited heterochromatization. Furthermore, 2 brains from patients aged 62 and 64 years, who died from malignant disease and in whom dementia was not a clinical feature, had normal heterochromatin content, although scattered plaques and tangles were present. Ten assays on this Intermediate Group of 5 brains revealed an average euchromatin content of 79.6 ± 5.0 SD per cent.

The duration of storage of the brains in the frozen state was not related to decreased euchromatin content. The average storage time at −90° C for Control brains was 121 days, Alzheimer brains 160 days, non-Alzheimer senile dementia 136 days and dialysis dementia 77 days. Preparations made within a few days of autopsy from Alzheimer affected brain also exhibited a reduced percentage of euchromatin. Furthermore storage of control brains at −90° C for up to 2.5 years did not alter the proportion of euchromatin. Finally, the average time between death and necropsy was examined and found not to be different among the groups. Therefore, the increase in heterochromatin content observed in both the presenile and senile brains associated with advanced Alzheimer histopathology does not appear to be related to age, terminal illness or the altered physiology associated with a non-Alzheimer type of dementia. Thus the decreased proportion of euchromatin found in Alzheimer's disease appears to be a functional state associated with this dementia process.

C. Chromatin Protein Content

The marked differences in the proportion of heavy chromatin following mechanical disruption could be related to the amount of protein bound to DNA. However, as shown in Table 3, there was no significant difference in the protein to DNA ratios for whole nuclei, heterochromatin, intermediate or light euchromatin fractions between presenile Alzheimer preparations and age-matched Controls, non-Alzheimer senile brains and senile dementias of the Alzheimer type. The light euchromatin fraction in all groups contained a lower protein to DNA ratio than

TABLE 3. AVERAGE PROTEIN TO DNA RATIOS OF NUCLEAR AND CHROMATIN FRACTIONS

				Protein/DNA g/g			
Group	*Age range*	*Brains*	*No. of preparations*	*Nuclei* $\bar{X}$ *SD*	*Hetero* $\bar{X}$ *SD*	*Intermediate* $\bar{X}$ *SD*	*Light euchromatin* $\bar{X}$ *SD*
Control 1	2–69	12	21	4.5±2.0	4.9±2.2	4.7±1.8	3.7±2.1
Control 2	53–69	5	7		4.4±1.6	4.1±1.4	3.0±1.4
Alzheimer	53–95	12	25	4.0±1.4	4.2±1.2	5.2±2.5	2.6±1.4
Presenile Alzheimer	53–69	6	11		4.1±0.0	5.6±2.3	2.6±1.3
Dialysis dementia	38–69	5	9	4.1±1.2	4.5±1.5	4.6±1.6	3.1±1.3
Intermediate	62–88	5	10	4.4±1.5	5.1±1.1	4.9±1.8	3.4±1.3

the other fractions. Examination of proteins in the chromatin fractions by electrophoresis revealed that the light euchromatin was depleted in histone H_1. Thus protein content alone cannot account for the increased amount of heavy chromatin found in Alzheimer brain.

D. Chromatin Conformation in Fractions Enriched in Glia and Neurons

In the neocortex of brains of patients with Alzheimer's disease senile plaques and neurofibrillary tangles are accompanied by loss of neurons and gliosis and the increase in heterochromatin could reflect an altered neuron to glia ratio. Therefore, an examination of the chromatin constituents from isolated nuclear preparations enriched in neurons or glia was undertaken in 2 Alzheimer affected brains and 7 Control brains. Since glia tend to have smaller nuclei than neurons, the nuclear size distribution was taken as a measure of extent of cell separation. In formalin-fixed sections of temporal lobe white matter stained with hæmotoxylin and eosin, the average glial nuclear diameter was found to be 3.8 μm ($n = 221$), whereas in the unfixed homogenate from Control brain, the average nuclear diameter for glia enriched fractions of cells prepared from the contralateral cerebral cortices was 3.3 μm ($n = 97$), and only 13 per cent of nuclei were greater than 6 μm. In contrast, the average nuclear diameter of the neuron enriched fraction was 9.0 μm ($n = 103$) and less than 16 per cent of the fraction was smaller than 6 μm in diameter. For 10 preparations from 7 Control brains, the euchromatin accounted for 64.4 ± 19.1 SD per cent of the total DNA in the glial enriched fraction and 81.7 ± 5.6 SD per cent in the neuron enriched fraction (Table 4).

TABLE 4. AVERAGE EUCHROMATIN CONTENT FOR NEURON AND GLIA ENRICHED FRACTIONS AND MIXED CORTICAL FRACTION

Group	*Age range*	*No. of brains*	*No. of preparations*	*Neurons* $\bar{X}$ *SD*	*Glia* $\bar{X}$ *SD*	*Whole cortex* $\bar{X}$ *SD*
Control	26–69	7	10	81.7± 5.6	64.4±19.1	75.2± 5.5
Alzheimer	63–67	2	7	63.1±17.6	38.5±13.6	55.6±16.8
Significance				$P < 0.01$	$P < 0.02$	$P < 0.01$

In glia enriched fractions from Alzheimer affected brain the nuclear diameter distribution was similar to that measured in preparations from control brains. However, the neuron enriched fraction from Alzheimer affected brains had a reduced proportion of nuclei greater than 12 μm in diameter (control = 19 per cent, Alzheimer 2 per cent) and an increased proportion of nuclei less than 6 μm in diameter (control = 16 per cent, Alzheimer 35 per cent). In addition, the isolated unfixed nuclei from Alzheimer brain generally were more deeply stained with toluidine blue than control nuclei.

Six glia enriched preparations from 2 Alzheimer dementia brains contained an average value of 38.5 ± 13.6 SD per cent euchromatin and 7 neuron enriched preparations contained 63.1 ± 17.6 SD per cent (Table 4).

Despite the difference in distribution of size of nuclei in the neuron enriched fraction in Alzheimer and Control preparations, the following calculation suggests that the neuron enriched nuclear fraction was not greatly contaminated by glia. Previous quantitative histopathological measurements of four cortical areas corresponding to Brodmann's areas 11, 21, 17 and 19 in two Control brains aged 54 and 65 years showed that neurons, on the average, accounted for 55 per cent of the total cells. In a case of Alzheimer's disease, aged 65 years, neurons accounted for 45 per cent of the total cells (Crapper, Dalton, Skopitz, Scott and Hachinski, 1975). Hence, a homogenate of Control cerebral cortex would contain 55 per cent neurons in which 81.7 per cent of the DNA would be in the euchromatin state and 45 per cent glia, containing 64.4 per cent euchromatin. Therefore, the homogenate would be expected to contain an average of 74 per cent euchromatin, a value close to the measured value of 75 per cent (Table 4). Assuming for Alzheimer affected brain that 45 per cent of the cells are neurons containing 63.1 per cent euchromatin, and 55 per cent of the cells are glia containing 38.5 per cent euchromatin, the homogenate would contain 49.5 per cent euchromatin. The measured value was 55.6 per cent for mixed cells and the satisfactory agreement between the measured and the predicted value from neuron and glia enriched fractions supports the possibility that an increase in the amount of heterochromatin occurred in both neurons and glia in the neo-cortex of brains from patients with advanced Alzheimer's disease.

E. Transcription of Chromatin In Vitro

Heterochromatin differs in efficiency from euchromatin as a template for transcription by the enzyme RNA polymerase. The transcription properties of the fractions prepared by sonication was studied. Using the method of Cedar and Felsenfeld (1972) the bacterial RNA polymerizing enzyme attaches to the template and elongation of the RNA chain is restricted by omitting one of the nucleotides from the incubation media. After fifteen minutes there is no further increase in RNA synthesis and the initiation reaction is stopped by the addition of $(NH_4)_2SO_4$ which prohibits reattachment of the enzyme. Propagation of RNA chains is then started by the addition of the missing nucleotide and $MgCl_2$. Both DNA and chromatin are soluble at every stage in this procedure.

Endogenous RNA polymerase activity was not present in these preparations because incorporation of nucleotide into RNA chains was not observed when the bacterial enzyme was omitted. Furthermore, heterochromatin offered no initiation sites for the bacterial enzyme in either control or Alzheimer affected material. In contrast, the production of RNA by Control human neuron enriched euchromatin (intermediate plus light euchromatin) fractions averaged 0.94 ± 0.7 pM of nucleotide incorporated per μg of DNA template (calculated as in Cedar and Felsenfeld, 1972) after fifteen minutes under chain initiation conditions and 1.25pM/μgDNA under elongation conditions (Table 5). In comparison to human euchromatin RNA production, calf thymus DNA was approximately five times more active. As shown in Table 5, euchromatin extracted from neuron enriched fractions from Alzheimer affected brains was closely similar in absolute incorporation of nucleotide per μg of template to preparations from age-matched controls. Employing *E. coli* RNA polymerase as a probe enzyme, these findings suggest that the increased proportion of DNA in heterochromatin in Alzheimer's disease may be in a conformational state which is also inaccessible to the naturally occurring RNA polymerase enzymes and hence may be of pathophysiological significance.

TABLE 5. AVERAGE NUCLEOTIDES INCORPORATION (pM/μg DNA) OF NEURON ENRICHED FRACTIONS AND MEAN RNA CHAIN LENGTH DISTRIBUTION

	Human control (*n* = 4) $\bar{X}$ *SD*	*Alzheimer* (*n* = 4) $\bar{X}$ *SD*	*Calf thymus*
Euchromatin			
Initiations	0.94 ± 0.70	1.14 ± 0.60	
Elongations	1.25 ± 0.60	1.27 ± 0.70	
DNA			
Initiations			1.98
Elongations			7.35
Mean RNA chain length (weight average)	1854	1967	

The RNA product of neuron enriched euchromatin was separated on the basis of chain length by centrifugation on continuous sucrose gradients. The average RNA chain length from a brain with Alzheimer's disease was not significantly different from age-matched controls (Table 5). The distribution of RNA chain lengths synthesized *in vitro* is shown in fig. 3 for representative experiments and the results indicate that the differences between the products formed from control and Alzheimer affected brain are not significant.

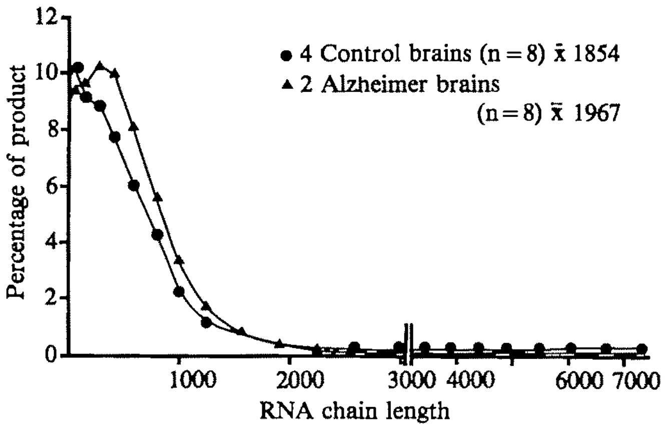

FIG. 3. Distribution of RNA chain length of *in vitro* transcription products of human neuron enriched euchromatin.

DISCUSSION

A. Chromatin Conformation

The disorder in brain metabolism underlying cell death and dysfunction in Alzheimer's disease is unknown. The possibility of a transmissible factor (Kidd, 1964; Gajdusek, 1977; De Boni and Crapper, 1978; Crapper and De Boni, 1978) and an environmental agent such as aluminium (Crapper *et al.*, 1976) have been considered. Whatever the primary pathogenic event, the decrease in euchromatin, separated by sonication and centrifugation as reported here, may be related to the observed decrease in cellular RNA and depressed protein metabolism. Whether the reduction in euchromatin is secondary to processes remote from the transcription of genetic information or a direct effect of the pathogenic process upon the genetic apparatus cannot be discerned from this study.

Transcription of chromatin with the bacterial enzyme RNA polymerase has been employed as a probe to evaluate the extent of separation of the chromatin constituents. This enzyme does not reflect transcription processes likely to occur *in vivo* by naturally occurring enzymes. However, the similarity in nucleotide incorporation and protein content for control and Alzheimer euchromatin fractions together with identical distributions of RNA chain length indicate that major alterations in the association of proteins with DNA have not occurred in Alzheimer's disease (Tables 5, 3 and fig. 3). These data also support the conclusion based on separation by centrifugation that in Alzheimer's disease the absolute amount of transcriptionally active DNA is reduced.

While changes in the accessibility of the DNA template within euchromatin may occur without heterochromatization, open helix within heterochromatin has never been observed (Frenster, Papalian, Masek and Frenster, 1978). This would suggest that the present observations further support the presence of reduced transcription in Alzheimer's disease. Increased nerve action potential activity is associated with increased RNA production (Hyden, 1962; Berry, 1969). In Alzheimer type dementia, it is possible that the average spike activity of surviving neurons has altered, resulting in decreased demands for transcriptionally active DNA. In this case the increase in heterochromatin could be considered to be secondary to the dementia process and unrelated to the pathogenesis of the disease. Although normal euchromatin content in dialysis and multi-infarct dementias argue against this position, neuron spike activity may differ among the dementias and hence this possibility cannot be completely excluded. Alternatively, reduced euchromatin may be important in the pathogenesis of the disease. For instance, deficits in hormone or metal ion metabolism within the brain could influence chromatin configuration (Leake, Trench and Barry, 1972; Finch and Klug, 1976; Thoma and Koller, 1978; Ryan and Potter, 1978). Mg^{2+}, Ca^{2+}, Mn^{2+}, Na^{+}, K^{+} and other trace metals are known to influence the amount of facultative heterochromatin. Altered phosphorylation or acetylation of chromatin proteins (Stein, Spelsberg and Kleinsmith, 1974) as well as cytoplasmic messengers are also important in the regulation of gene expression. Hence a systematic examination of factors regulating gene expression in Alzheimer's disease will be necessary before the physiological significance of the measured decrease in euchromatin is satisfactorily explained.

While neuron-glia interactions have long been observed (Hyden, 1962) it is nevertheless surprising that both neurons and glia undergo heterochromatization in Alzheimer's disease. This may indicate a more widespread disorder in cerebral metabolism than previously anticipated.

A wide range of heterochromatin content was found over the cerebral hemispheres in each of the terminal cases of Alzheimer's disease. The proportion of neurons with neurofibrillary degeneration and the density of senile plaques also varies widely in different regions of the cerebral cortex (Crapper, Dalton, Skopitz, Scott and Hachinski, 1975; Crapper, *et al.*, 1976). Cells exhibiting heterochromatization must occur in a large proportion of the population in order to influence the overall average value. Therefore the possibility must be considered that brains without clinical dementia but with restricted Alzheimer type pathology have some degree of heterochromatization in a small proportion of cells.

SUMMARY

Chromatin samples were prepared from forty human brains. Chromatin was separated into a heavy heterochromatin fraction and two euchromatin fractions: intermediate euchromatin and light euchromatin. Employing a bacterial RNA polymerase as probe, only the euchromatin fractions were capable of RNA synthesis.

In Control human brains, in brains of patients with dialysis dementia and in brains of elderly individuals without or with dementia of a type other than

Alzheimer's disease, the euchromatin fractions accounted for about 75 per cent of the total DNA. In contrast, in brains of patients with advanced senile dementia or presenile dementia of the Alzheimer type, a wide range of euchromatin content was encountered with an average value of 55 per cent. Heterochromatization occurred in both neuron and glia enriched fractions suggesting that a major alteration in protein metabolism occurs in Alzheimer's disease.

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REFERENCES

ALTMAN, J. and LERMAN, L. S. (1970) Kinetics and intermediates in the intracellar synthesis of bacteriophage T4 deoxyribonucleic acid. *Journal of Molecular Biology*, **50**, 235-261.

BERRY, R. W. (1969) Ribonucleic acid metabolism of a single neuron: correlation with electrical activity. *Science, Washington*, **166**, 1021-1023.

BOWEN, D. M., SMITH, C. B. and DAVISON, A. N. (1973) Molecular changes in senile dementia. *Brain*, **96**, 849-856.

—— —— WHITE, P., GOODHARDT, M. J., SPILLANE, J. A., FLACK, R. H. A. and DAVISON, A. N. (1977*a*) Chemical pathology of the organic dementias. I. Validity of biochemical measurements on human post-mortem brain specimens. *Brain*, **100**, 397-426.

—— —— —— FLACK, R. H. A., CARRASCO, L. H., GEDYE, J. L. and DAVISON, A. N. (1977*b*) Chemical pathology of the organic dementias. II. Quantitative estivation of cellular changes in post-mortem brains. *Brain*, **100**, 427-453.

CEDAR, H. and FELSENFELD, G. (1972) Transcription of chromatin *in vitro*. *Journal of Molecular Biology*, **77**, 237-254.

CRAPPER, D. R., DALTON, A. T., SKOPITZ, M., SCOTT, J. W. and HACHINSKI, V. C. (1975) Alzheimer degeneration in Down Syndrome. Electrophysiologic alterations and histopathologic findings. *Archives of Neurology, Chicago*, **3**, 618-623.

—— and DE BONI, U. (1978) Brain aging and Alzheimer's disease. *Canadian Psychiatric Association Journal*, **23**, 229-233.

—— KRISHNAN, S. S. and QUITTKAT, S. (1976) Aluminium, neurofibrillary degeneration and Alzheimer's disease. *Brain*, **99**, 67-80.

DAYAN, A. D. and BALL, M. J. (1973) Histometric observations on the metabolism of tangle-bearing neurons. *Journal of Neurological Sciences*, **19**, 433-436.

DE BONI, U. and Crapper, D. R. (1978) Paired helical filaments of the Alzheimer type in cultured neurons. *Nature, London*, **271**, 566-568.

FINCH, J. T. and KLUG, A. (1976) Solenoidal model for superstructure in chromatin. *Proceedings of the National Academy of Sciences, USA*, **73**, 1897-1901.

FLEISCHER-LAMBROPOULOS, H. and REINSCH, I. (1971) Protein biosynthesis in Rattenhirnzellkernen. *Hoppe-Seyler's Zeitschrift für Physiologische Chemie*, **352**, 593-602.

FRENSTER, J. A., PAPALIAN, M. M., MASEK, M. A. and FRENSTER, J. H. (1978) Persistent euchromatin after DNA template inactivation. *Journal of Cell Biology*, **79**, 110A. Abstract.

GAJDUSEK, D. C. (1977) Unconventional viruses and the origin and disappearance of Kuru. *Science, Washington*, **197**, 943-960.

HYDEN, H. (1962) Cytophysiological aspects of the nuclei acids and proteins of nervous tissue. In: *Neurochemistry*. Edited by K. A. C. Elliot, I. H. Page and J. H. Quastel. Springfield: Charles C. Thomas, pp. 331-375.

KIDD, M. (1964) Alzheimer's disease—an electron microscopical study. *Brain*, **87**, 307-319.

LEAKE, R. E., TRENCH, M. E. and BARRY, J. M. (1972) Effect of cations in the condensation of hen erythrocyte nuclei and its relation to gene activation. *Experimental Cell Research*, **71**, 17-26.

LEVY, L., LEVY, S., ROSENBERG, S. A. and SIMPSON, R. T. (1973) Selective stimulation of nonhistone chromatin protein synthesis in lymphoid cells by phytohemagglutinin. *Biochemistry*, **12**, 224-228.

LOWRY, O. H., ROSENBROUGH, N. J., FARR, A. L. and RANDALL, R. J. (1951) Protein measurement with the folin phenol regent. *Journal of Biological Chemistry*, **193**, 265-275.

MANN, D. M. A. and SINCLAIR, K. G. A. (1978) The quantitative assessment of lipofuscin pigment, cytoplasmic RNA and nucleolar volume in senile dementia. *Neuropathology and Applied Neurobiology*, **4**, 129-135.

RINGBORG, U. (1966) Composition of RNA in neurons of rat hippocampus at different ages. *Brain Research, Amsterdam*, **2**, 296-298.

RYAN, T. and POTTER, H. D. (1978) A Mg^{2+} dependent class of thick filaments and correlated nuclear chromatin in catfish photoreceptors. *Journal of Neurocytology*, **7**, 313-321.

SCHEIBEL, A. B. and TOMIYASU, U. (1978) Dendritic sprouting in Alzheimer's presenile dementia. *Experimental Neurology*, **60**, 1-8.

STEIN, G. S., SPELSBERG, T. C. and KLEINSMITH, L. S. (1974) Nonhistone chromosomal proteins and gene regulation. *Science, Washington*, **183**, 817-824.

SUZUKI, K., KATZMAN, R. and KOREY, S. R. (1965) Chemical studies on Alzheimer's disease. *Journal of Neuropathology and Experimental Neurology*, **24**, 211-224.

THOMA, F. and KOLLER, T. H. (1978) The ionic strength dependence of chromatin folding. In: *Electronmicroscopy*, Vol. II. *Biology*. Ninth International Congress on Electronmicroscopy, Toronto. Edited by J. M. Sturgess. Toronto: The Microscopical Society of Canada, pp. 220-221.

YASMINEH, W. G. and YUNIS, J. J. (1970) Localization of mouse satellite DNA in constitutive heterochromatin. *Experiment Cell Research*, **59**, 69-75.

(*Received November 29, 1978*)

Brain (1979), **102**, 497-508

OPPOSED ADDUCTING SACCADES IN CONVERGENCE-RETRACTION NYSTAGMUS

A PATIENT WITH SYLVIAN AQUEDUCT SYNDROME

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INTRODUCTION

CONVERGENCE-RETRACTION nystagmus is a well-recognized sign of pretectal involvement, but why it occurs is still a matter of speculation. It had been concluded from electromyographic data that these distinctive ocular movements result from synchronous innervation of opponent pairs of rectus muscles (Breinin, 1957; Gay, Brodkey and Miller, 1963). We have recorded and analysed the amplitude-velocity relationship of rapid components of this type of nystagmus by high resolution oculography to answer the question whether the lateral and medial rectus muscles were innervated synchronously, as claimed, or reciprocally.

CASE HISTORY

Our patient was an alert 33-year-old man exhibiting progressive left-sided hyperæsthesia of the face, limbs and trunk for seven months, and who had difficulty in reading and double vision for three months. He had typical pretectal localizing signs: pupillary light reactions were sluggish, all upward eye movements above 15 degrees were absent, and convergent eye movements occurred spontaneously after single refixation saccades, especially after saccades upward or during gaze at downward-moving optokinetic stimuli. His ocular pursuit was saccadic and interrupted occasionally by convergent jerks of the eyes. During saccades to the side, his abducting eye undershot while his adducting eye either attained or overshot its target (fig. 2A). A compulsory involuntary blink accompanied each downward saccade.

Computer tomographic examination of the patient's brain revealed a right-sided thalamic tumour that extended inferiorly into the rostral midbrain (fig. 1). After a six-month course of chemotherapy and irradiation, he suddenly lost vision, had a generalized convulsion and died.

At necropsy the tumour in the thalamus was necrotic and œdematous. It extended into the posterior third ventricle and aqueduct. It was centred in the pineal base, and involved portions of the collicular

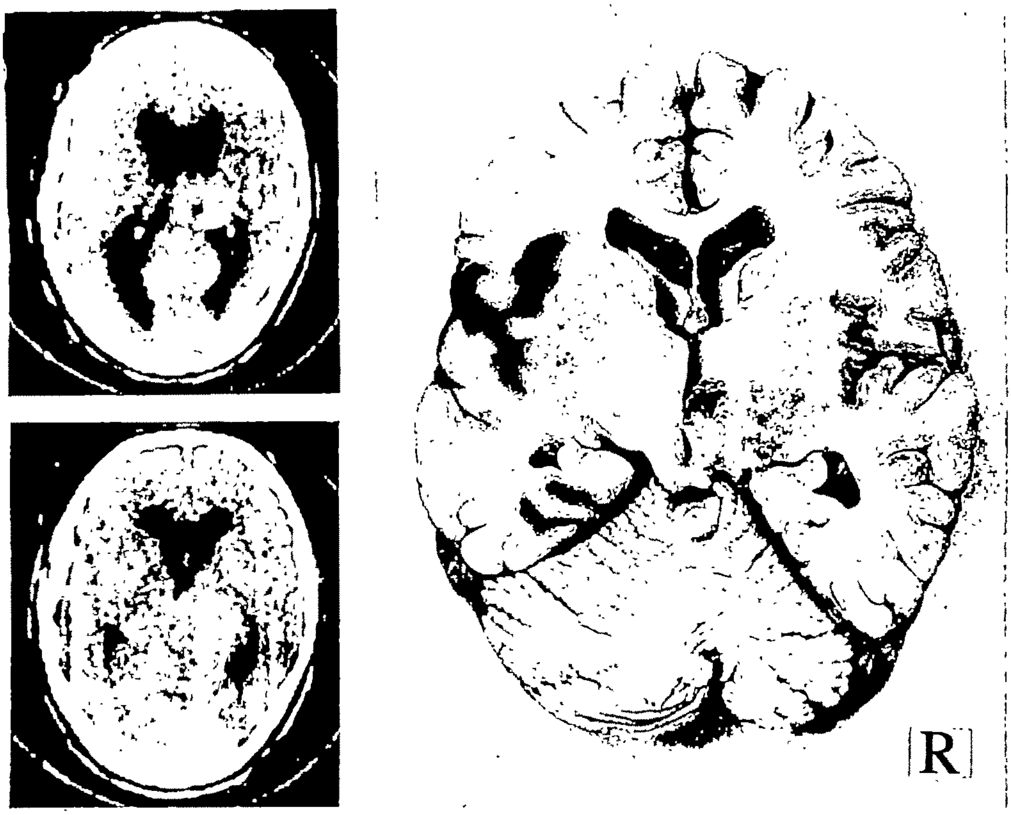

FIG. 1. Views from contrast enhanced computer tomogram taken eight weeks following eye movement recordings (*left*) and brain on post-mortem examination (*right*). Bleeding about left insula occurred as result of a fall at time of death.

plate and the internal capsule (fig. 1). Cerebellum was spared. Microscopically the tumour cells, though greatly altered by the therapy and the pre-mortem autoinfarction, were presumed to be of glial origin and of malignant character.

METHODS

Horizontal movements were monitored by reflected infra-red illumination from each eye by the method of Stark, Vossius and Young (1962) and as described from our laboratory by Selhorst, Stark, Ochs and Hoyt (1976). Horizontal signals were tape recorded for detailed analysis. Simultaneous vertical movements were measured in the right eye by monitoring the electro-oculographic (EOG) potential with electrodes placed above and below the eye. The patient sat in a chair with a head-rest and viewed targets one metre away. High magnification Super-8 cine films were taken at 24 frames per second frontally and from each side as the patient viewed an upward and downward moving optokinetic nystagmus (OKN) stimulus. Ocular retraction accompanying OKN-elicited movements could be measured from projections of the lateral view cine films.

Tape recordings of horizontal eye movements were analysed by the following procedure. Line frequency interference was removed with a comb filter consisting of three narrow ($Q = 10$) band-reject filters centred at 60, 120 and 240 Hz. The comb filter introduced negligible distortion as determined by observing the electrical difference between unfiltered and filtered noise-free saccadic signals. Velocity tracings were obtained with standard analog differentiation techniques. The high-frequency roll-off of the differentiators was set at -6 dB/octave and began at 180 Hz. Saccadic velocities so determined were identical to those computed by digital techniques. Eye position and velocity signals were then displayed on a Elema-Schonander, Mingograf EEG machine. This polygraph uses ink jets rather than pens and can usefully display frequencies in excess of 600 Hz.

Saccadic initiation synchrony was measured by determining the point where the velocity trace of each eye departed from the resting noise level. The differentiators were set at a very high gain (25 deg/s = 1 cm) and low-pass post-filtered at 70 Hz to improve readability. The Mingograf was run at a chart speed of 600 mm/s to attain a precision of 1 ms.

The data presented was obtained at the time the patient began a course of radiation and chemotherapy. Follow-up oculographic recordings were also made six months later, four days before the patient's death. Oculomotor performance was essentially unchanged.

RESULTS

Recordings of the horizontal and vertical components of eye movements as the patient responded to an upward shift of the target (fig. 2B) showed an upward movement accompanied by rapid, opposed, large amplitude, adducting movements, followed by smaller oscillations. Single downward saccades were markedly slowed and accompanied by several adductive oscillations (fig. 2C). As the patient viewed

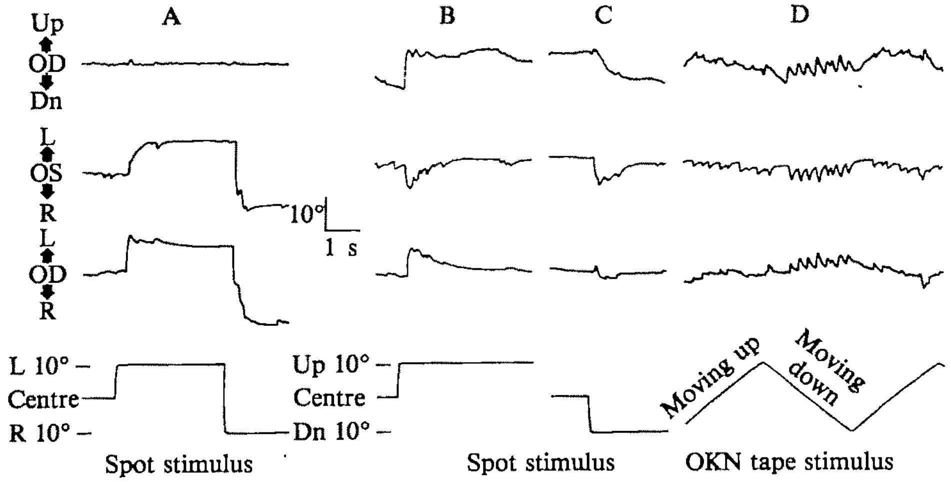

FIG. 2. Horizontal and vertical eye position tracings. A, response to a horizontal saccadic stimulus showing asymmetry of saccade amplitude, leaving eyes transiently converged. Note opposed quick adducting movements during fixation. B, response to an upward saccadic stimulus showing convergent movements evoked by normal upward saccades. Opposed adduction saccades ensue. C, response to a downward saccadic stimulus showing asymmetrical opposed convergent movements with slow downward movements. D, response to projected optokinetic nystagmus stripes. Note sequence of opposed adduction saccades.

downward-moving optokinetic stripes, the recordings showed oblique upward-convergent nystagmus (fig. 2D). Response to upward moving stripes elicited similar convergent nystagmus of lower amplitude (fig. 2D).

Peak velocity was plotted against magnitude for these adductions and following abductions (fig. 3). The upper solid line in this figure represents the normal curve for saccades recorded under similar conditions, and the lower solid line is the normal curve for vergence and glissadic movements (Bahill, Clark and Stark, 1975*a*, *b*).

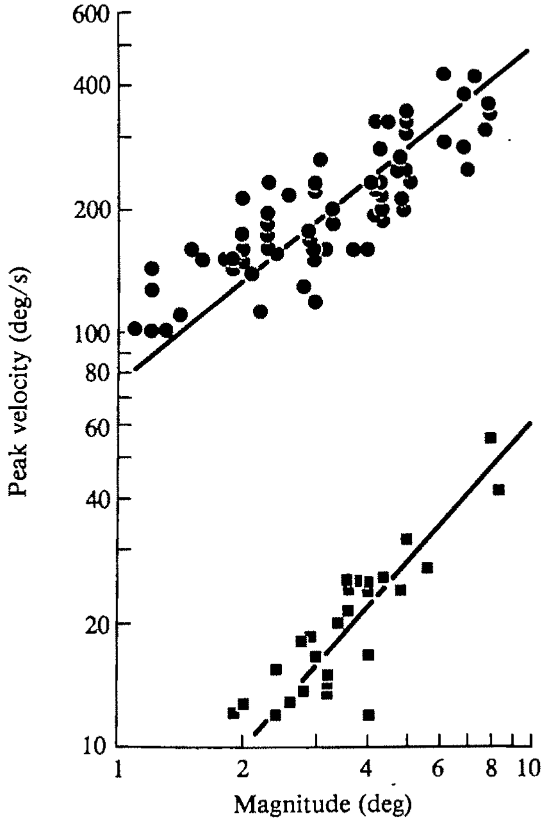

FIG. 3. Peak velocity of opposed adducting saccadic movements (●) and opposed abducting glissadic movements (■) as a function of the magnitude of the movement. Upper solid line indicates normal peak velocity curve for saccades and lower line, for vergence and glissadic movements.

The fit between these two normal curves and the measurements from this patient clearly shows that the opposed adductions have velocities of normal saccades, while the abductions have velocities of glissades. This figure includes measurements of horizontal motions elicited by intentional upward saccades, non-intentional post-saccadic movements, and by downward-moving optokinetic nystagmus stimuli. There is no systematic difference between the saccadic velocities evoked in these separate manœuvres.

Opposed saccadic adduction is a remarkable violation of Hering's law of equal innervation (for less dramatic examples, in normal subjects, *see* Bahill, Ciuffreda, Kenyon and Stark, 1976). To investigate this violation, we performed a detailed analysis of the horizontal eye movements. Examination of saccadic fine structure revealed numerous pairs of normal conjugate saccades and opposed adducting saccades. In addition, there were several other saccadic patterns, best described as intermediate. Selected examples representing the range of paired saccadic structure are shown in fig. 4. Example A is a normal pair of conjugate saccades; examples B and C are intermediate; and examples D, E and F are pairs of opposed adducting saccades. All the initial saccades displayed in fig. 4, as well as the immediately following, oppositely directed saccades, have magnitude-velocity characteristics which cluster closely about the normal main sequence saccadic curve (fig. 3, upper solid curve). On the time scale of fig. 4, slower glissadic movements cannot be discerned.

Examples E and F in fig. 4 are representative of pairs of opposed adducting saccades. In example E, the saccade in the left eye preceded its opposite by 8 ms, and in F followed by 5 ms. Saccadic initiation asynchrony, with an average value of 8 ms, was a constant feature of opposed adducting saccades, in contrast to the impressive synchrony of this patient's conjugate saccades. The initiation synchrony

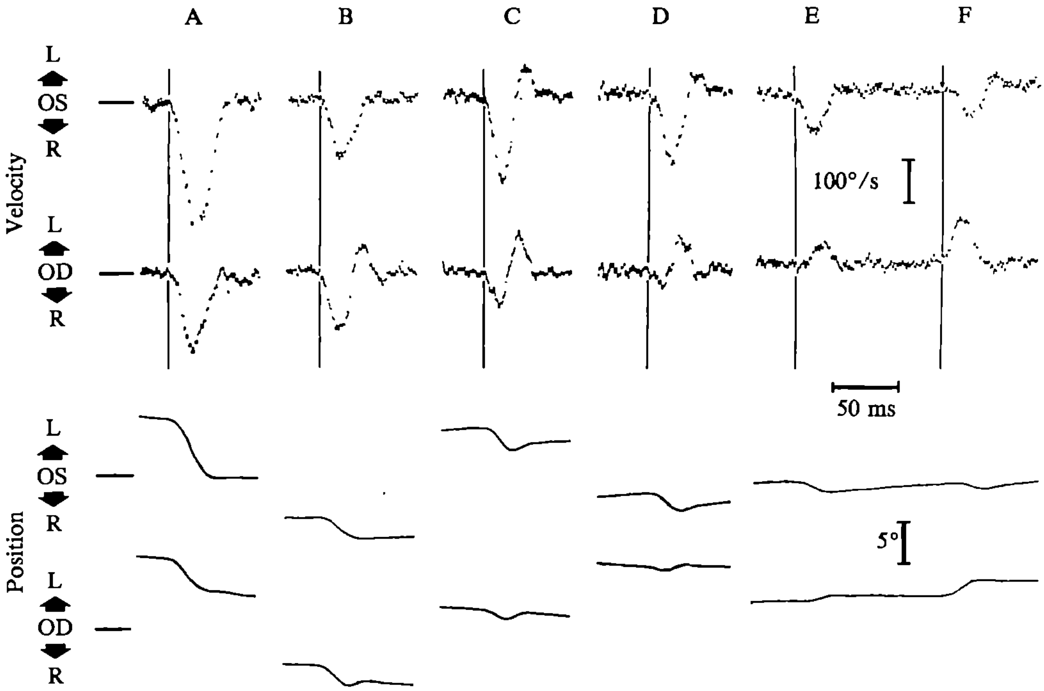

FIG. 4. Selected saccadic eye movements. Stimulus conditions were: A and B, horizontal smooth pursuit; C, E and F, fixation following a vertical saccade; D, vertical optokinetic nystagmus. *See text* for discussion of this sequence of wave-forms.

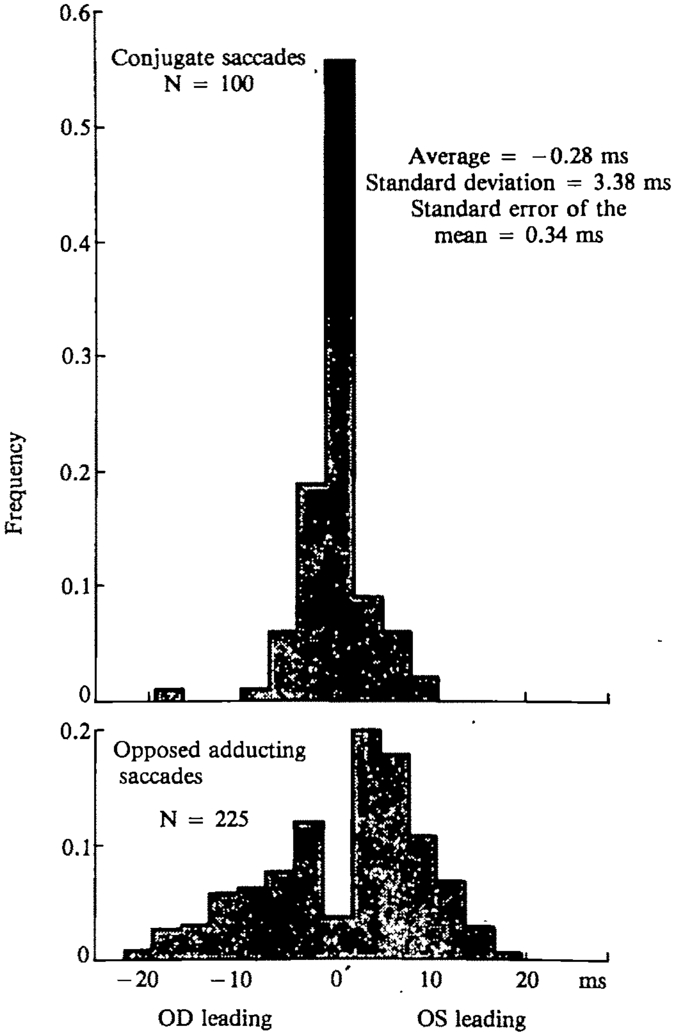

FIG. 5. Synchrony histograms of conjugate saccades and opposed adducting saccades. Small conjugate saccades elicited by horizontal smooth pursuit (N = 100). Opposed adducting saccades elicited by horizontal smooth pursuit (N = 75), by vertical optokinetic nystagmus (N = 75), and by attempted fixation (N = 75). Synchrony estimated to nearest ms and grouped into bins 3 ms wide.

of 100 conjugate saccades is illustrated in fig. 5 (*upper*). The average of these measurements is within one standard error of the mean. Williams and Fender (1977) published similar data on conjugate saccades of a normal subject. (The larger of two conjugate saccades was generally observed to start first).

The asynchronous pattern of opposed adducting saccades is shown in the lower curve of fig. 5. Its bimodal curve indicates an obligate asynchrony. With few exceptions, one eye leads the other; the first of the pair is usually the larger (for example, figs. 5E and F).

Analysis of cine films of the patient's eyes with slow motion projection as viewed from in front showed the oblique motion to follow an approximate trajectory 50 degrees from horizontal. No cyclorotatory movements were evident in either eye. Analysis of lateral views using frame-by-frame projection of adduction saccades induced by downward moving optokinetic stimuli did not show retraction of the globe. During the adducting and upward saccadic motion, the anterior corneal surface moved no more than 0.3 mm, the limit of resolution of our method. In contrast, a blink caused 1 mm of ocular movement.

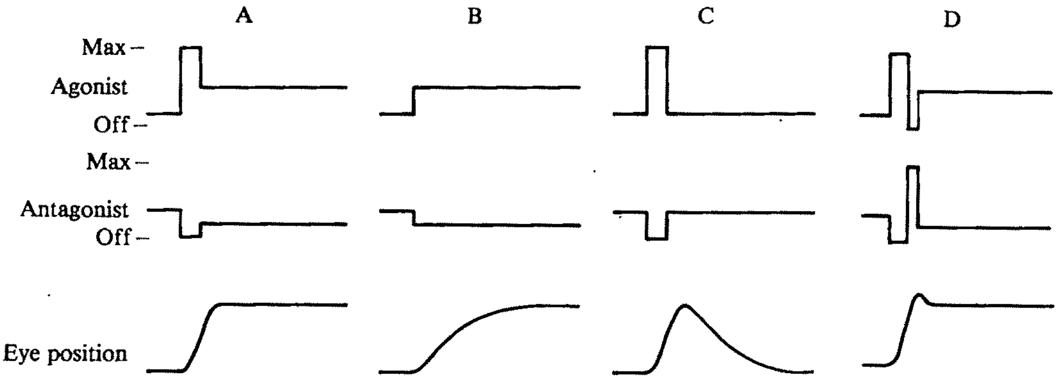

FIG. 6. Agonist and antagonist monocular innervation patterns with resulting eye movements for A, normal horizontal saccades. B, normal vergence movements. C, opposed adducting saccadic movements followed by glissade. D, dynamic overshoot complex.

DISCUSSION

Dodge (1903) recorded and identified several distinct types of eye movements defined by their velocities. Saccades are produced by reciprocal pulses of maximum activation of agonist neurons and of total inhibition of antagonist neurons, causing the highest possible velocities (fig. 6A). Duration of this pulse determines the magnitude of a saccade. Vergence movements are considerable slower. They result from simple shifts or steps in tonic firing rate of agonist and antagonist motoneurons (fig. 6B). Glissades, more recently defined, have the same velocities as vergences, but unlike vergences that depend on a visual input signal, they have no latency (Bahill *et al.*, 1975*b*). Saccadic and glissadic movements are stereotyped in that, for a given magnitude, peak velocities cannot be altered by voluntary effort and variation between subjects is small. Thus, normal innervation can be assumed for a particular saccade or vergence movement having these identifying peak velocity-magnitude relationships.

This conclusion from eye movement dynamics agrees with studies of oculomotor nuclei in animals (Schaefer, 1965; Robinson, 1970; Fuchs and Luschei, 1970;

Reinhart and Zuber, 1971; Keller and Robinson, 1971), electromyographic recordings in humans (Miller, 1958, 1959; Tamler, Marg, Jamplosky and Nawratzki, 1959) and bioengineering models of the orbit and eye muscles (Cook and Stark, 1968; Clark and Stark, 1974; Collins, 1975). These rules apply equally to vertical as well as horizontal saccades (Feinstein and Williams, 1972; Henn and Cohen, 1973; Bahill and Stark, 1975).

The discovery that the opposed adductions in our patient have the velocities of main sequence saccades implies that normal reciprocal mechanisms of innervation are involved. Breinin (1957), Esslen and Papst (1961), and Gay, Brodkey and Miller (1963) published electromyograms of retraction nystagmus; with expanded time scale recordings the latter recognized alternating 10 to 30 ms bursts of reciprocal excitation and inhibition of lateral and medial rectus muscles, and indicated that the fast opposed movements had features of saccades and were not at all vergence-like.

The opposed adduction movements are immediately followed by slow abducting glissades without latency. These glissades apparently result from pulse-step mismatch in which the pulse innervation is not followed by corresponding 'step' innervation. The normal, although slow, glissadic velocities indicate agonists and antagonists have reciprocally innervated tonic motoneuronal firing rates.

A normal saccadic programme often includes a small movement in the reverse direction at the end of the primary movement, a *dynamic overshoot* (Bahill, Clark and Stark, 1975*c*) (fig. 6D). These dynamic overshoots are often monocular. Velocity and magnitude of dynamic overshoots fall on the main sequence plot for saccades (fig. 3, upper solid curve). These rapid saccadic reversals are to be distinguished from slower glissadic reversals (Weber and Daroff, 1972; Bahill *et al.*, 1975*b*). Dynamic overshoots were frequently observed following the conjugate saccades of our patient (fig. 4B, OD). As suggested by Bahill *et al.* (1975C), the innervation reversal underlying dynamic overshoot (fig. 6D) is not determined by visual feedback, but by time optimal programming strategy. A similar suggestion has been made with respect to voluntary nystagmus by Shults, Stark, Hoyt and Ochs (1977).

We propose that opposed adducting saccades documented in our patient arise out of the dynamic overshoot mechanism. To illustrate how this could occur, we have arranged the series of examples (fig. 4) showing smooth transition between conjugate saccades (A), saccades with small dynamic overshoot (B), saccades with dynamic overshoots larger than the primary movement (C and D), and finally, opposed adducting saccades (E and F). The pattern of innervation for such a binocular pair of saccades is diagrammed in fig. 7. They are synchronous initially. The left eye completes a saccade with a small dynamic overshoot, while the right eye reverses direction almost immediately.

The early reversal of innervation in the right eye produces the major dynamic (overshoot) component which is opposed in direction to the primary component of the left eye. The resulting movements are thus opposed. If this explanation is correct,

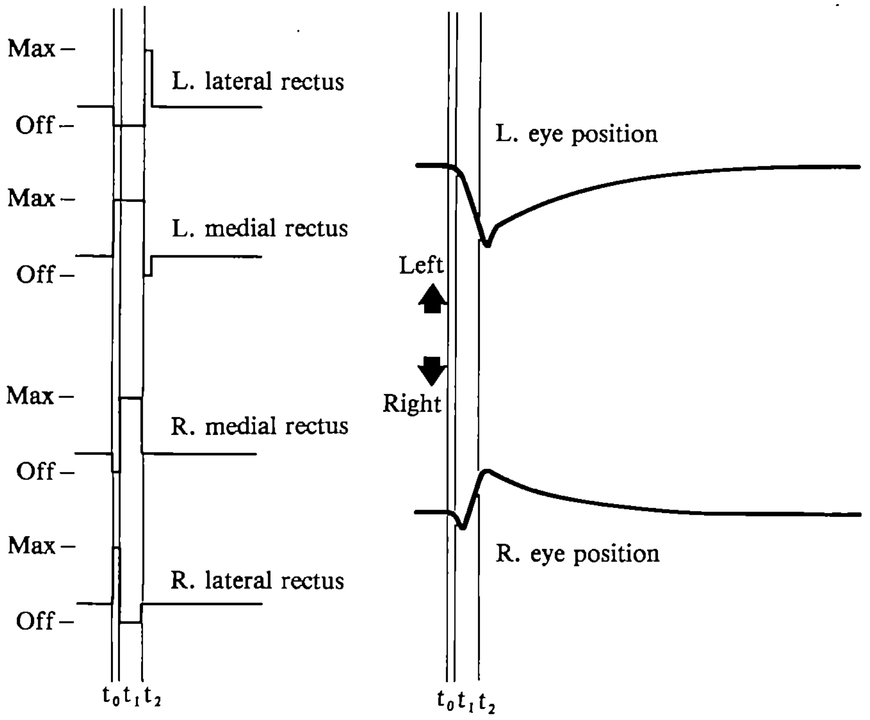

FIG. 7. Innervation pattern to produce opposed adductor saccades. Firing rates as functions of time (*left*) for neurons supplying indicated horizontal rectus muscles as shown on right. Initially, at t_0, innervation pattern produces conjugate saccadic components. Then, at t_1, exaggerated dynamic overshoot-like reversal of innervation for right eye produces large opposed adduction saccadic component. Next, at t_2, left eye innervation reverses for a dynamic overshoot. Finally, opposed abduction glissades complete eye movement pattern after innervation returns to tonic levels. Innervation and movement based upon saccadic pair of fig. 4c.

then there must be a small initiation asynchrony between the major (opposed) movements in the two eyes in this condition. The saccadic synchrony histogram derived from our patients recordings (fig. 5) confirm this prediction. Electromyographic records published by Gay, Brodkey, and Miller (1963) also show this asynchrony.

Although the analogy to dynamic overshoot explains how an intact lower level saccadic mechanism might produce opposed saccades, further explanation is required for occurrence of horizontal or oblique movements when the patient tries to look upward. Lesions in the pretectal area block control signals for vertical movement. The brain's adaptive response to the resulting gaze paresis is to increase gain, that is, to increase effort and innervation. Helmholtz' student, Laminsky (1869), observed that most vertical movements in normal subjects have small horizontal components. Bahill and Stark (1975), in their study of vertical movements, found a spectrum of horizontal saccadic phenomena, including prominent dynamic overshoot components and a range of initiation asynchronies. How would high gain, secondary to vertical paresis, affect these horizontal components? We believe that our patient's opposed adducting saccades represent the answer to this question —it would cause increased amplitude and asynchrony in the framework of the dynamic overshoot mechanism. Thus our analysis suggests that normal lower level brain-stem channels, modified by the high gain signals they are conveying, are the explanation for so-called 'spread of excitation' hypothesized correctly on clinical grounds (Cogan, 1959; Smith, Zieper, Gay and Cogan, 1959; Segarra and Ojeman, 1961). The oculographic findings confirming reciprocal innervation on these horizontal eye movement components explain in our patient the absence of retraction movements of the globe. Similarly, the patient studied electromyographically by Gay, Brodkey and Miller (1963) also had tightly-ordered reciprocal innervation. The neurophysiological basis for ocular retraction movements observed in some patients with the Sylvian Aqueduct Syndrome awaits explication.

SUMMARY

We report high resolution oculographic recordings on a patient with convergent-retraction nystagmus (Parinaud's Sign). Recordings show opposed adducting saccades which are slightly asynchronous (8 ms), in contrast to the conjugate horizontal saccades which are exactly synchronous (0.3 ms). Normal saccadic velocity of these opposed adductions necessarily implies reciprocal innervation of horizontal and vertical agonist-antagonist pairs. Lateral view cine films show absence of retraction, apparently as a consequence of normal orbital mechanics. We suggest that normal mechanisms for dynamic overshoot saccades are involved in the production of these abnormal opposed adducting saccades.

ACKNOWLEDGEMENTS

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REFERENCES

BAHILL, A. T., CIUFFREDA, K. J., KENYON, R. and STARK, L. (1976) Dynamic and static violations of Hering's law of equal innervation. *American Journal of Optometry and Physiological Optics*, **53**, 786–796.

—— CLARK, M. R. and STARK, L. (1975*a*) The main sequence, a tool for studying human eye movements. *Mathematical Biosciences*, **24**, 191–204.

—— —— —— (1975*b*) Glissades—eye movements generated by mismatched components of the saccadic motoneuronal control signal. *Mathematical Biosciences*, **26**, 303–318.

—— —— —— (1975*c*) Dynamic overshoot in saccadic eye movements is caused by neurological control signal reversals. *Experimental Neurology*, **48**, 107–122.

—— and STARK, L. (1975) Neurological control of horizontal and vertical components of oblique saccadic eye movements. *Mathematical Biosciences*, **27**, 287–298.

BREININ, G. M. (1957) Electromyography—a tool in ocular and neurologic diagnosis. *Archives of Ophthalmology*, **57**, 165-167.

CLARK, M. R. and STARK, L. (1974) Control of human eye movements: II. A model for the extraocular plant mechanism. *Mathematical Biosciences*, **20**, 213-238.

COGAN, D. G. (1959) Convergence nystagmus. *Archives of Ophthalmology*, **62**, 295-299.

COLLINS, C. C. (1975) The human oculomotor control system. In: *Basic Mechanisms of Ocular Motility and Their Clinical Implications*. Edited by G. Lennerstrand and P. Bach-Y-Rita. New York: Pergamon Press.

COOK, G. and STARK, L. (1968) The human eye-movement mechanism. *Archives of Ophthalmology*, **79**, 428-436.

DODGE, R. (1903) Five types of eye movement in the horizontal meridian plane of the field of regard. *American Journal of Physiology*, **8**, 307-329.

ESSLEN, E. and PAPST, W. (1961) Die Bedeutung der Elektromyographie für die Analyse von Motilitätsstörungen der Augen. *Bibliotheca Ophthalmologica*, **57**, 1-168.

FEINSTEIN, R. and WILLIAMS, W. J. (1972) Interactions of the horizontal and vertical human oculomotor systems: the saccadic systems. *Vision Research*, **12**, 33-44.

FUCHS, A. F. and LUSCHEI, E. S. (1970) Firing patterns of abducens neurons of alert monkeys in relationship to horizontal eye movements. *Journal of Neurophysiology*, **33**, 382-392.

GAY, A. J., BRODKEY, J. and MILLER, J. E. (1963) Convergence retraction nystagmus. *Archives of Ophthalmology*, **70**, 456-461.

HENN, V. and COHEN, B. (1973) Quantitative analysis of activity in eye muscle motoneurons during saccadic eye movements and positions of fixation. *Journal of Neurophysiology*, **36**, 115-126.

KELLER, E. L. and ROBINSON, D. A. (1971) Absence of a stretch reflex in extraocular muscles of the monkey. *Journal of Neurophysiology*, **34**, 908-919.

LAMINSKY, S. (1869) Evaluation of the angular velocity of saccadic eye movements. *Pflügers Archivs*, **2**, 418.

MILLER, J. E. (1958) Electromyographic pattern of saccadic eye movements. *American Journal of Ophthalmology*, **46**, Part II, 183-186.

—— (1959) The electromyography of vergence movements. *Archives of Ophthalmology*, **62**, 790-794.

REINHART, R. J. and ZUBER, B. L. (1971) Abducens nerve signals controlling saccadic eye movements in the cat. *Brain Research, Amsterdam*, **34**, 331-344.

ROBINSON, D. A. (1970) Oculomotor unit behavior in the monkey. *Journal of Neurophysiology*, **33**, 393-404.

SCHAEFER, K. P. (1965) Die Erregungsmuster einzelner Neurone des Abducens-Kernes beim Kaninchen. *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere*, **284**, 31-52.

SEGARRA, J. M. and OJEMAN, R. J. (1961) Convergence nystagmus. *Neurology, Minneapolis*, **11**, 883-893.

SELHORST, J. B., STARK, L., OCHS, A. L. and HOYT, W. F. (1976) Disorders in cerebellar ocular motor control: 1. Saccadic overshoot dysmetria: an oculographic, control system and clinico-anatomic analysis. *Brain*, **99**, 497-508.

SHULTS, W. T., STARK, L., HOYT, W. F. and OCHS, A. L. (1977) Normal saccadic structure of voluntary nystagmus. *Archives of Ophthalmology*, **95**, 1399-1404.

SMITH, J. L., ZIEPER, I., GAY, A. J. and COGAN, D. G. (1959) Nystagmus retractorius. *Archives of Ophthalmology*, **62**, 864-867.

STARK, L., VOSSIUS, G. and YOUNG, L. R. (1962) Predictive control of eye tracking movements. Institute of Radio Engineers Transactions on Human Factors in Electronics. *HFE-3*, 52-57.

TAMLER, E., MARG, E., JAMPLOSKY, A. and NAWRATZKI, I. (1959) Electromyography of human saccadic eye movements. *Archives of Ophthalmology*, **62**, 657-661.

WEBER, R. B. and DAROFF, R. B. (1972) Corrective movements following refixation saccades: type and control system analysis. *Vision Research*, **12**, 467-475.

WILLIAMS, R. A. and FENDER, D. H. (1977) The synchrony of binocular saccadic eye movements. *Vision Research*, **17**, 303-306.

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Brain (1979), **102**, 509–526

PARTICIPATION OF THE STRETCH REFLEX IN HUMAN PHYSIOLOGICAL TREMOR

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INTRODUCTION

RECENT studies in cat (Matthews and Stein, 1969; Poppele and Bowman, 1970; Matthews, 1972; Goodwin, Hulliger and Matthews, 1976) emphasize that, in resting muscles, primary spindle endings have a higher dynamic sensitivity to small than to larger changes in muscle length. In man, a similar high dynamic sensitivity of spindle response to minute length changes is present and is probably enhanced during voluntary contraction (Vallbo, 1973*a*, *b*; Burke, Hagbarth, Lõfstedt and Wallin, 1976; Burke, Hagbarth and Löfstedt, 1978*b*), suggesting that dynamic as well as static fusimotor neurons are co-activated with skeletomotor neurons. For example, during isometric voluntary contraction the response of primary endings to vibration is enhanced (Burke *et al.*, 1976); during maintenance of posture, primary endings increase or decrease their activity following sudden small changes in load (Struppler and Erbel, 1971; Struppler, Burg and Erbel, 1973; Burke, Hagbarth and Löfstedt, 1978*a*); and during slow voluntary movements the response of primary endings to small irregularities in speed attests to their ability to detect small deviations from the desired speed (Vallbo, 1973*a*; Burke *et al.*, 1976). During relaxation after an isometric contraction, human primary endings are often activated by the slight lengthening which occurs (Vallbo, 1970; Burg, Szumski, Struppler and Velho, 1973; Hagbarth, Wallin, Burke and Lõfstedt, 1975).

Moreover, the alterations in spindle discharge resulting from such small perturbations of muscle length may affect the discharge of motoneurons at a latency compatible with monosynaptic action (Struppler and Erbel, 1971; Evarts and Bizzi, 1976; Binder and Stuart, 1979; Vallbo, Hagbarth, Torebjörk and Wallin, 1979). In particular, bursts of increased spindle discharge alternating with synchronized pauses in spindle afferent input (as occurs during muscle vibration) may, by monosynaptic action, produce marked synchronization of discharges from an active motoneuron pool (Homma, Kanda and Watanabe, 1972; Desmedt and Godaux, 1975; Hagbarth, Hellsing and Löfstedt, 1976; Vallbo *et al.*, 1979).

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In healthy subjects actively holding the hand and fingers in an outstretched position, an 8–12 Hz action tremor of low amplitude can be recorded by sensitive goniometers attached to the finger or wrist joints. This so-called 'physiological tremor' can be enhanced under certain circumstances, as with anxiety or during fatigue (for reviews *see* Freund and Dietz, 1978; Marsden, 1978; Shahani and Young, 1978), and the oscillations can also be temporarily enhanced by a brisk tap on the moving parts (Lippold, 1970). A number of recent studies have addressed the question whether physiological tremor is primarily dependent on central neural mechanisms generating rhythmical synchronized motor activity, or on peripheral factors such as unfused contractions of asynchronously discharging motor units and mechanical resonance at frequencies inherent in the tremulous system (Allum, Dietz and Freund, 1978; Freund and Dietz, 1978). In particular, a much debated question is whether the segmental stretch reflex plays an essential role in the genesis of physiological tremor. Freund and Dietz (1978) and Lance and McLeod (1975) think not, though they disagree as to whether the tremor arises from central or peripheral factors. Marsden (1978) agrees with earlier suggestions of Halliday and Redfearn (1956), Lippold, Redfearn and Vuco (1957) and Lippold (1970) that the stretch reflex does contribute to physiological tremor. The evidence on which these conclusions are based was necessarily somewhat indirect.

Our aim was to record muscle spindle afferent activity and electromyographic (EMG) activity from human finger and wrist flexors during physiological tremor and to answer three main questions. (a) Are the primary spindle endings in the contracting muscles sensitive enough to respond to the often very minute movements of physiological tremor? (b) If so, are the resultant fluctuations in afferent activity followed, at monosynaptic latency, by similar fluctuations in skeletomotor outflow? (c) Are these EMG bursts accompanied by signs of fusimotor coactivation (as in voluntary tremor-like movements or quick twitch-like contractions (Hagbarth, Wallin and Löfstedt, 1975; Vallbo *et al.*, 1979)) or by signs of spindle unloading (as with tendon-jerk or tonic-vibration-reflex contractions (Burg *et al.*, 1973; Hagbarth, Wallin, Löfstedt and Aquilonius, 1975; Burke *et al.*, 1976))?

The spindle afferent and EMG records obtained during normal physiological tremor were compared with patterns seen during physiological tremor enhanced by fatigue, and during the damped oscillatory accentuations of the tremor rhythm caused by sudden, brisk mechanical displacements of the outstretched fingers (Lippold, 1970). Comparisons were also made with the spindle and EMG patterns seen when passive oscillatory length changes were superimposed upon a contracting muscle (Sommer, 1941; Berthoz and Metral, 1970; Neilson and Neilson, 1978).

MATERIALS AND METHODS

Data were obtained from 8 experiments in 2 healthy subjects during which 19 recordings of neural activity, identified as being of muscle spindle origin, were made from fascicles of the left median nerve innervating wrist flexors (5 multi- and 2 single unit recordings), finger flexors (5 multi- and 4 single unit recordings), wrist pronators (1 multi- and 1 single unit recording) and abductor pollicis brevis (1 single unit recording). For reasons discussed below, illustrations are taken from multi-unit recordings. As judged by their response to electrically-induced muscle twitches (*vide infra*), the multi-unit recordings were seen to be dominated by signals in group Ia afferent fibres, and the single units were identified as spindle afferents. Neural activity was recorded with 0.2 mm tungsten microelectrodes tapered to a tip of 1-5 microns, insulated by several coats of lacquer and inserted percutaneously. Amplification, enhancement of signal-to-noise ratio by filtering and amplitude discrimination, integration of multi-unit neural activity (time constant 0.01 s), and display techniques were the same as have been published previously (Hagbarth, Hongell, Hallin and Torebjörk, 1970; Hagbarth, Wallin and Löfstedt, 1975), except that a TECA Instagraph (FOR 4) was used. Raw data were also recorded on a four-channel FM Instrumentation tape recorder from which they were replayed for subsequent detailed analysis on TECA direct recording paper, the contrast of which was heightened by making copies by green light (Xerox model No. 3100). Activity from successive tremor cycles was superimposed either by triggering the Instagraph sweep internally from the mechanical signal or by manually superimposing Xerox transparencies of individual cycles and Xeroxing the resultant group. EMG signals were recorded from two TECA monopolar needle electrodes inserted a few millimetres apart into the area of the same muscle from which the spindle afferent signals came. Great care was taken to be certain the EMG electrodes were accurately positioned so that a meaningful correlation could be made between EMG and muscle spindle activity. Muscle contractions often have different effects on the spindles in the active portions of the muscle than on spindles somewhat remote from the area of contraction (Vallbo, 1970; Hagbarth, Wallin and Löfstedt, 1975).

Wrist or finger joint position was recorded by a goniometer constructed around a special low-noise, low-inertia potentiometer with a conductive plastic element (Bourns No. 66375-1). The arms of the goniometer (each 9.5 g in weight and 14.5 cm in length) were strapped tightly to the appropriate regions. The mass and moment of inertia (665 g cm^2) of the goniometer arms were very small in relation to the mass of the hand (450–500 g in our subjects) or loads of 40 to 2500 g applied to the hand (*see* Young and Hagbarth, 1980) so that mechanical resonances due to the goniometer seem unlikely. Potential changes from the potentiometer were amplified and recorded either as DC signals or, when higher gains were necessary during 'isotonic' movement, by using an AC circuit with time constant 0.33 s (low frequency cut-off approximately 0.5 Hz). Torque produced by isometric contraction of the flexor muscles was recorded from the hand or fingers by the attachment in the proper plane of specially designed metal fittings to a Grass model FT10C Force Transducer, whose element formed one arm of a bridge circuit. Grass SPA-1 accelerometers were also taped to the finger or hand at times.

During experiments, the subject lay supine on a comfortable couch in a warm room with the extended and abducted left arm resting on a foam cushion support reaching to the wrist, the unsupported supinated hand being held outstretched against gravity. The goniometer was attached to record tremulous movements either at the wrist joint or at the interphalangeal or metacarpophalangeal joints. Wrist movements were recorded with a light (10 g) splint strapped to the palmar aspect of the hand to immobilize the metacarpo- and interphalangeal joints in extension, and metacarpophalangeal movements were recorded with the interphalangeal joints held extended by the splint. To hold the splinted hand against gravity in an outstretched position (180 degrees at the wrist joint) the subject had to maintain a weak contraction in the wrist flexor muscles, and the recordings of wrist tremor were made under such conditions without any extra weight attached to the hand. To obtain a weak contraction in the finger flexor muscles, the fingers had to be loaded with an extra weight (40 g), and most recordings of finger tremor were made with such an extra weight attached.

The subjects were instructed to exert only as much motor effort as necessary to hold the hand and fingers in the given position, without stiffening the joints by co-contractions in antagonistic extensor muscles. Electrical twitches were produced by 0.5 ms square-wave pulses delivered from a Grass stimulator through the EMG electrodes. Brisk taps (of the order of 40 ms in duration) to the board over the dorsal or palmar aspect of the hand provided sudden changes in length of the contracting wrist flexor muscles by moving the hand approximately 0.5 degrees at the wrist. Passive, small-amplitude, roughly sinusoidal flexion-extension movements of the wrist were made manually by the experimenter who monitored the goniometer signal.

RESULTS

During these studies, records were made of both single and multi-unit neural activity which was demonstrated respectively to be exclusively or predominantly the afferent discharge of muscle spindle endings. Because these studies of tremor were particularly concerned with (1) the temporal relationship between the start or finish of spindle afferent activity and associated EMG bursts and (2) obtaining an estimate of the overall spindle activity, we have emphasized the results of the multi-unit recording technique. In this way one samples the activity of a number of spindle afferent fibres, but while the 'integrated activity' gives a better measure than single unit recordings of the overall spindle inflow, it is difficult to exclude the possibility that signals from, for example, low threshold Pacinian corpuscles may contribute to the stretch-evoked afferent discharges. However, the multi-unit recordings were evidently dominated by signals in group Ia afferents, as judged by their dynamic responses to passive muscle stretch, silence during passive muscle shortening, and typical responses to electrically-induced muscle twitches (a pause during the contraction with discharge during the relaxation phase (Szumski, Burg, Struppler and Velho, 1974; Hagbarth, Wallin and Löfstedt, 1975)). Careful analysis of the well-classified single unit data revealed no differences in spindle behaviour from that evidenced by multi-unit recordings. We were not able to recognize motor volleys in the neurograms.

Non-enhanced Physiological Tremor

The physiological tremor of wrist and fingers recorded during the first few minutes after the subject had raised his supinated hand to the outstretched position was regularly of low amplitude, the angular deviations seldom exceeding 0.1 degrees. Still, there was characteristically an obvious grouping of afferent spindle discharges from the contracting wrist and finger flexor muscles, with bursts of spindle impulses occurring mainly during the stretch phases of the tremor cycles and relative silence during the shortening phases. The EMG activity simultaneously recorded from the receptor-bearing flexor muscles did not reveal any obvious similar grouping of motor unit potentials. The contrast between the tremulous rhythmical activity in the neurogram and the relative lack of similar rhythmicity in the EMG was obvious in both visual (fig. 1) and auditory (loud-speaker) displays of the signals. Besides illustrating a spindle sensitivity high enough to sense tremulous wrist movements of less than 0.1 degree, fig. 1 shows another characteristic feature of the afferent stretch discharges: their 'intensity' is not directly proportional to the amplitude of any given tremor cycle. Even the smallest tremulous movements, barely discernible in the goniometer trace, were often accompanied by distinct stretch discharges.

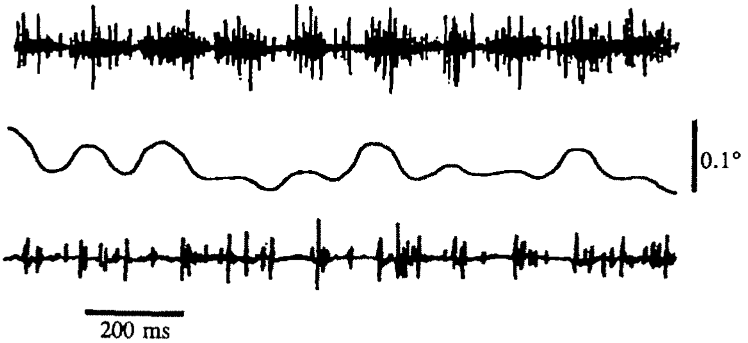

FIG. 1. Afferent responses (*upper trace*) to barely perceptible physiological tremor at the wrist (*middle trace*) under isotonic conditions. Note the clearly visible rhythmic activity in the spindle-dominated multi-unit neural recording from a wrist flexor muscle, though no obvious grouping of EMG activity is seen in the same muscle (*lower trace*). The goniometer record (*middle trace*) is arranged so that flexion of wrist moves the line upward. The neural bursts occur during the phase of the tremor cycle when wrist flexors are being stretched.

Tremor Enhanced by Fatigue

By means of different manœuvres, to be described more extensively in a separate report (Young and Hagbarth, 1980), the amplitude of the physiological tremor could be increased; a grouping of the EMG potentials in the flexor muscles then became obvious. One of these manœuvres consisted of letting the subject hold his hand outstretched for five to twenty minutes, with or without extra loads temporarily placed in the palm or on the fingers. As the subject began to feel fatigued the amplitude of finger and wrist tremor was enhanced, the angular deviations at the wrist often varying between 0.2–0.5 degrees (with the hand unloaded). This enhanced tremor was accompanied by a marked grouping, not only of the afferent spindle discharges but also of the EMG potentials in the wrist flexor muscles. Superimposition of tremor cycles illustrates a delay or phase lag of approximately 20 ms between the afferent neural and EMG events (fig. 2). This delay was about

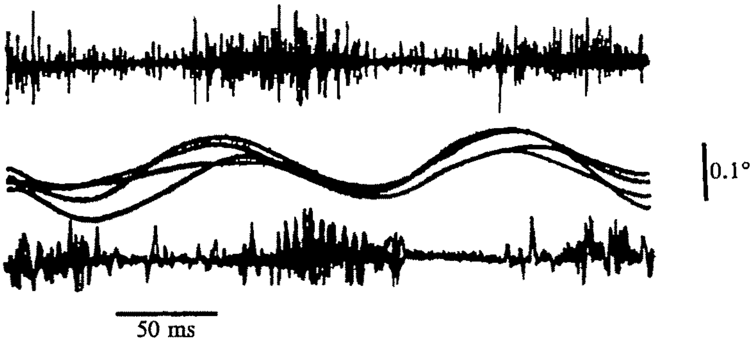

FIG. 2. Afferent responses in 4 superimposed spindle-dominated multi-unit neural recordings (*upper trace*) from a wrist flexor muscle during spontaneous isotonic enhanced physiological tremor after the hand had been held outstretched against gravity for fifteen minutes. Goniometer as in fig. 1. Note that groups of afferent stretch discharges in the nerve are followed approximately 20 ms later by comparable groups of EMG discharges (*lower trace*).

the same for finger or wrist flexor muscles. As in non-enhanced tremor (fig. 1), the neural bursts here also usually reached a peak during the first half of the stretch phases, whereas relative neural silence was most apparent in the midst of the shortening phases. The EMG bursts, on the other hand, reached their peak during the latter part of the stretch phases and ended at the beginning of the shortening phases. These tremulous movements appear, therefore, to be 'ballistic' in the sense that the flexor muscles were electrically silent during the major part of the shortening phase, the contractions of flexors apparently serving to increase flexor muscle tension at the end of each extension phase.

Tremor Temporarily Enhanced by Mechanical Perturbations

The background physiological tremor could be temporarily enhanced by various sudden perturbations of the tonically contracting flexor muscles, for example, by a quick tap on the outstretched hand (fig. 3A), a brisk voluntary muscle 'twitch'

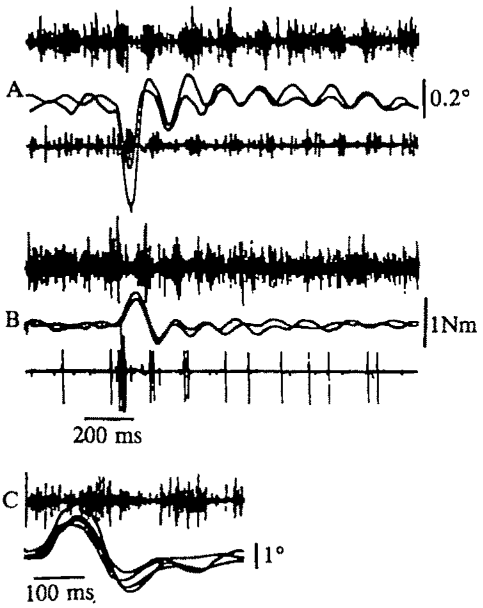

FIG. 3. Superimposed records of afferent responses in spindle-dominated multi-unit neural activity (*upper trace* of A, B and C) from a wrist flexor muscle in association with enhanced physiological tremor triggered in different ways. EMG activity in the same muscle is seen on the lower trace of A and B. In A, single sharp taps in the palm of the outstretched hand produce the large initial deflection in which the goniometer (*middle trace*) records movement in the direction of wrist extension. The low-amplitude pre-existing physiological tremor is accentuated by the evoked oscillation which is then damped. Note that the neural stretch discharges are followed approximately 20 ms later by EMG bursts signalling stretch reflex modulation of the motor outflow. In B, recorded under isometric conditions, sudden single 'voluntary twitches' of the wrist flexors produce a damped oscillation of torque (cal. middle trace = 1 Newton metre) in which the neural stretch discharges are followed in approximately 20 ms by EMG bursts. In C, single electrically induced twitches of the wrist flexor muscle under isotonic conditions produce shortening (cal. for goniometer on lower trace is 1 degree) which unloads the spindles. Because of the non-linearity of spindle sensitivity, the bursts of spindle-dominated multi-unit neural activity are especially prominent during the early part of the stretch or lengthening phase, and the spindle discharge is very similar both in response to this large initial stretch and to the much smaller second stretch phase of the triggered tremor.

(fig. 3B), or an electrically induced muscle twitch of the flexor muscles (fig. 3C). As Lippold (1970) noted, using the first of these perturbations, the perturbing stimulus triggered oscillations which rapidly declined in amplitude until the tremulous movements were back to their original amplitude—though the phase of physiological tremor had now been reset by the stimulus. The oscillations were more quickly damped in the isometric situation when the subject exerted flexion force against the strain gauge (fig. 3B) than in the standard isotonic situation, when the unloaded hand was held outstretched against gravity with no external objects hindering the pendular wrist movements. Closer inspection of fig. 3A and B reveals that the rhythmical spindle discharges, occurring during each stretch phase of the damped oscillations, were followed by EMG bursts, the latency between afferent and EMG events also being approximately 20 ms, as during the spontaneous tremor shown in fig. 2. As is also clearly seen in fig. 3A and C, the 'intensity' of the afferent stretch discharges is not directly proportional to the amplitude and/or speed of the corresponding stretch movements, suggesting that the primary endings possess a higher dynamic sensitivity to small than to large stretch movements. Because of the larger amplitude of the superimposed movement, the EMG bursts are differently timed in relation to the movement cycle in small as compared to larger amplitude movements. In the large initial oscillations immediately following a perturbing stimulus, there was a tendency for the neural and EMG bursts to occur earlier during the movement cycles than in the succeeding lower amplitude pendular movements. Note, for instance, how the repetitive EMG bursts in fig. 3A, following the initial stretch reflex response, progressively shift from the early part towards the later part of the stretch phases as the triggered oscillatory movement is gradually damped.

Spindle and EMG-patterns during Passive Sinusoidal Stretching of Contracting Flexor Muscles

The patterns of spindle afferent and EMG activity during physiological tremor were compared with the patterns seen when the contracting wrist and finger flexor muscles were stretched sinusoidally by passively applied joint movements at 6–9 Hz to mimic the tremor rhythm (fig. 4). As first demonstrated by Sommer (1941), such sinusoidal muscle stretch, during a voluntary attempt to maintain a constant contraction, produces a synchronization of the EMG activity to the movement cycles (fig. 4A). Bursts of electrical activity alternating with periods of relative silence were seen both in the neurogram and in the EMG, the bursts in the neurogram reaching their peaks in the early part of the stretch phases and preceding those in the EMG by about 20 ms. Thus, the timing of the mechanical, neural and EMG events were similar to the timing seen during enhanced physiological tremor (compare fig. 2 and fig. 4A). When the subject was instructed to relax, and his hand was supported entirely by the experimenter so that no postural muscle contraction was necessary, the flexor muscles usually remained EMG-silent during the passive alternating movements (fig. 4B). Only occasionally did EMG responses at latencies of about 20 ms occur at the end of the stretch phases (fig. 4C); their occurrence did not appear to be directly related to the intensity of afferent spindle bursts (compare fig. 4B and C).

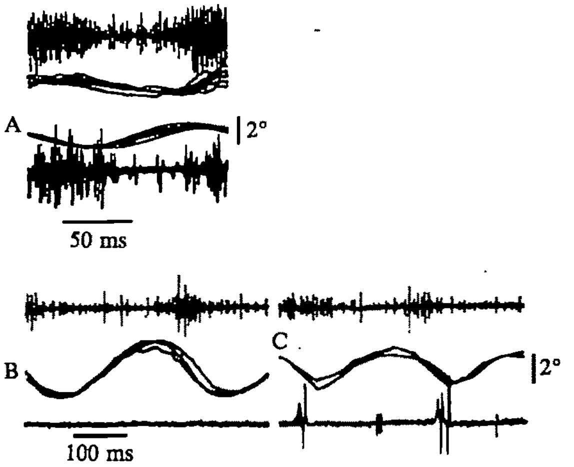

FIG. 4. Recordings from a wrist flexor muscle (neural activity, upper trace; EMG, lower trace) during passive alternating flexion-extension movements of the wrist signalled by a goniometer (next to bottom line). In A, passive 7 Hz movements are superimposed upon a moderate voluntary-sustained background contraction (second trace is an integrated plot of neural activity). The spindle afferent stretch discharge is followed 20 ms later by an EMG discharge as in fig. 2. In both B and C the subject tries to remain relaxed but in C an EMG discharge follows the spindle-dominated multi-unit stretch discharge seen in the neural recording in each group.

Spindle and EMG-patterns during Voluntary Fast Alternating Movements

A pattern of spindle activity which differed from that seen during spontaneous tremor or passive sinusoidal movements appeared during voluntary fast alternating wrist or finger movements. In agreement with previous studies (Vallbo, 1973*b*; Hagbarth, Wallin and Löfstedt, 1975) it was found that two bursts of spindle discharges usually occurred during single voluntary 'twitch' contractions; an early discharge slightly delayed in relation to the initial EMG bursts and a second discharge occurring during the stretch phase following the twitch (fig. 5A). Spindle contraction discharges alternating with spindle stretch discharges were seen also during fast voluntary alternating movements of the wrist and fingers (fig. 5B). With increased speed of the alternating movements (up to about 6 Hz), the stretch and contraction discharges tended to merge (fig. 5C and latter part of fig. 5B), producing a more sustained, less rhythmical spindle afferent inflow than that seen during spontaneous tremor or passive alternating movements where only stretch discharges could be seen (compare fig. 5C with fig. 2 and fig. 4A).

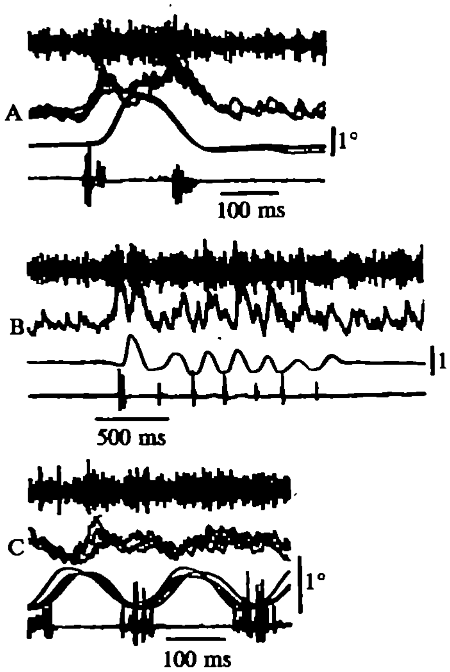

FIG. 5. Recording from the flexor muscle to the distal phalanx of the index finger during voluntary alternating movements. The upper trace in each is the spindle-dominated multi-unit neural activity, the second trace is the integrated neural activity (time constant 0.02 s), the third is the goniometer signal (cal = 1 degree) from the distal interphalangeal joint and the bottom trace is EMG activity from the same muscle. In A, superimposed records of single fast 'voluntary twitches' of the finger flexor: a spindle 'contraction discharge' is seen to accompany the voluntary EMG activity and a spindle stretch discharge occurs on the falling phase of the mechanogram. In B, which depicts the sudden start and finish of voluntary alternating flexion and extension movements, contraction discharges are seen in the neural record. Stretch discharges can also be seen in the nerve even in response to the remaining mechanical oscillations after the voluntary movements have stopped. In C, superimposed recordings during fast (5 Hz) voluntary tremulous movements, spindle afferent 'contraction discharges' typical of alpha-gamma co-activation and stretch discharges can still be seen.

DISCUSSION

Small Tremulous Movements Sensed by Primary Spindle Endings

Our results support Lippold's suggestion (1970) that 'physiological tremor will also involve stretch receptor activation in phase with it'. As illustrated in fig. 1, the primary spindle endings in a normally contracting muscle are sufficiently sensitive to respond during the stretch phases, even when the tremulous movements are of such low amplitude that they are barely visible to the naked eye. Though their significance was not recognized at the time, tremulous afferent discharges from muscles without clearly visible tremulous movements were mentioned in an early microneurographic study (Hagbarth and Vallbo, 1968). The high dynamic sensitivity of spindle endings to minute perturbing stimuli has also been shown in single unit recordings, where primary endings may respond to arterial pulse waves within a relaxed human muscle (Burke, Hagbarth and Wallin, 1979; Burke, Skuse and Stuart, 1979). This afferent response may follow each pulse wave; it does not reflect spindle discharge in response to so-called 'normal resting tremor' (Brumlik and Yap, 1970), the passive tremulous oscillation of the body with skeletal muscles at rest which is due to cardiorespiratory forces—a modified ballistocardiogram (BCG). The amplitude of this subclinical BCG tremor is less than 10 per cent that of physiological tremor, and it is still unknown whether spindle endings are sensitive enough to respond to these tremulous oscillations of relaxed muscle.

Physiological tremor, however, is by definition an action tremor, present only when the muscles are contracting. For purposes of discussion, we include all action tremors found in normal subjects under the term 'physiological tremor'. As previously emphasized (Granit, 1955; Struppler and Erbel, 1971; Burke *et al.*, 1978*a*, *b*), the static fusimotor drive during voluntary or postural contractions provides the spindle endings with a background discharge which enables them to respond in a two-directional way to muscle length changes: not only with increased firing to stretch but also with decreased firing to unloading or muscle shortening. Thus, the rhythmical spindle activity illustrated in fig. 1 should probably not be regarded merely as a series of repetitive stretch responses, but as alternating stretch and unloading responses from fusimotor-driven primary spindle endings.

Lack of Apparent EMG Synchronization in Low Amplitude Physiological Tremor

The lack of apparent EMG grouping in recordings like that shown in fig. 1 cannot be taken as conclusive evidence that there is no trend at all for the motor unit discharges to occur more frequently during one particular phase of the tremulous movements. However, the present findings agree with previous evidence (Marshall and Walsh, 1956; Dietz, Bischofberger, Wita and Freund, 1976; Elble and Randall, 1976; Allum *et al.*, 1978) that low amplitude physiological tremor is not dependent on motor synchronization but on peripheral factors, such as unfused contractions of asynchronously discharging motor units, with the stiffness of the contracting muscles and the inertia of the moving parts influencing the resonant frequency of the system.

The Segmental Stretch Reflex as a Temporal Modulator for Motor Outflow in Enhanced Physiological Tremor

When the amplitude of physiological tremor is enhanced by fatigue or by perturbations applied to the contracting muscle, the tremulous fluctuations in spindle afferent activity are followed after 20 ms or so by similar fluctuations in motor outflow to the receptor bearing muscles (figs. 2 and 3). This delay for finger or wrist flexor muscles corresponds roughly to the latency of the monosynaptic segmental stretch reflex for these muscles. The latency of 'finger jerks' varies with arm length and type of mechanical stimulus, but it is safe to say that the EMG changes in our experiments follow the alterations in afferent volleys at a latency appropriate for segmental spinal reflex action. This latency is too short for the operation of long-loop reflexes whose participation in the 'functional stretch reflex' control of postural muscle contractions has recently been stressed (Lee and Tatton, 1975; Evarts and Vaughn, 1978; Marsden, Merton, Morton, Adam and Hallett, 1978). Such longer latency responses to perturbations superimposed upon contracting muscles are undoubtedly effective ultimately in the control of muscle performance, particularly in response to larger displacements; but the evidence presented here emphasizes that with smaller displacements, as in the case of enhanced physiological tremors, the segmental stretch reflex does play an important role as 'temporal modulator' for these tremors, causing synchronization of the motor outflow to flexor muscles so that EMG bursts occur at the end of extension phases. Of interest in this connection are the studies of Vilis and Cooke (1976) in monkeys, indicating that the contribution of the segmental stretch reflex to modulation of the so-called functional stretch reflex is relatively greatest when perturbations of a tonically contracting muscle are small.

However, rather than being regarded simply as a series of repetitive stretch reflexes, the mechanism of enhanced physiological tremor (as illustrated by the events in fig. 2) should probably be considered as a reflex modulation of the voluntarily maintained motor outflow (hence the term 'temporal modulator'). The rhythmical volleys of (and pauses in) spindle inflow would be responsible for excitability fluctuations in the firing motoneuron pool. These fluctuations would affect the precise timing of the motor impulses, there being an increased probability for motoneuron discharges to occur during periods when Ia volleys impinge upon the pool. The segmental stretch reflex seems to exert a similar modulating influence upon the motor discharges when passively applied oscillatory movements are superimposed upon a steady voluntary contraction (compare figs. 2 and 4A). Grouping of EMG activity in synchrony with the passive movements occurs in a fashion similar to that when motor discharges are 'time-locked' to the mechanical waves during vibration of a muscle or its tendon (Homma, *et al.*, 1972; Desmedt and Godaux, 1975; Hagbarth *et al.*, 1976; Burke and Schiller, 1976). In all three instances, the synchronized rhythmical inflow from spindles produces, via the segmental stretch reflex arc, rhythmical fluctuations of excitability in the firing motoneuron pool which are of sufficient amplitude to produce 'clustering' of motor impulses in synchrony (allowing for the necessary phase lag) with the movement cycles. Though the possibility that long-loop 'stretch reflex' arcs also participate in this modulation of the motor outflow (Marsden, 1978; Neilson and Neilson, 1978) cannot be definitely excluded, the short phase lag between the neural and EMG events in our recordings gives no support to that assumption.

It cannot be inferred, however, that the grouping of motor discharges in enhanced physiological tremor depends solely on excitability changes resulting from tremulous spindle inflow. Because of the normal hypo-excitable phase following each motoneuron discharge (relative refractoriness, Renshaw inhibitory feedback, autogenetic Golgi inhibition and so forth—compare Shahani and Young, 1973), there will be intervening periods when motoneuron discharges are less likely to occur, particularly if groups of motoneurons discharge more or less synchronously and these hypo-excitable periods coincide with the phases of reduced spindle inflow. Furthermore, it is reasonable to suppose that the Ia afferent volleys from flexor muscles simultaneously exert a reciprocal inhibitory effect upon antagonistic extensor motoneurons; and, *vice versa*, that afferent stretch discharges from extensors during each movement cycle should contribute to the EMG pauses in flexor muscles. In the present study, simultaneous recordings from antagonistic extensor muscles were not made, but there is little reason to doubt that the spindle discharges from these muscles occur out of phase with those from the flexors. Previous observations (Shahani and Young, 1976, 1978) indicate that EMG bursts may appear to be synchronous in antagonistic muscle groups in the forearm during essential-type action tremor; but this topic needs further investigation, special care being taken to make selective EMG recordings from true antagonists operating at the same joint.

The Segmental Stretch Reflex as a Positive Feed-back in Enhanced Physiological Tremor

The movements in enhanced physiological tremor (fig. 2) are, like voluntary fast alternating movements, apparently ballistic in the sense that the muscles are electrically silent and, according to calculations based upon the relationship between EMG activity and tension produced in muscle, are mechanically relaxed during the greater part of the shortening phase; the flexor muscle contractions produce an increase in muscle tension at the end of each extension phase, which stops the ongoing movement and propels the hand or finger back in the opposite direction. In this way, the rhythmical motor outflow, which is phase-locked to the rhythmical spindle inflow, accentuates the pre-existing tendency of the system to oscillatory behaviour by producing muscle contractions which are appropriately timed in relation to the movement cycles to enhance the tremor amplitude. This is in agreement with the positive feedback theory of Halliday and Redfearn (1956).

The Segmental Stretch Reflex as a Negative Feed-back for Larger Amplitude Oscillatory Movements

The following question should be asked: can the same segmental stretch reflex mechanisms, which appear to be a driving force behind spontaneous tremulous movements of smaller amplitude in enhanced tremor, also serve to damp oscillatory movements of larger amplitude, initiated by sudden perturbations of musclé (Crago, Houk and Hasan, 1976; Neilson and Neilson, 1978)? That this may indeed be the case is suggested by recordings such as fig. 3A, where the reflex EMG bursts are differently timed in relation to the movement cycle in movements of smaller as opposed to larger amplitude. This differential timing may be a consequence of the fact that human primary spindle endings possess a higher dynamic sensitivity to small than to large changes in length (compare figs. 1 and 3C), a property demonstrated for cat muscle spindles by Matthews and Stein (1969) and Poppele and Bowman (1970). Because of this non-linearity of the primary endings, the peak of the afferent stretch discharge (and the resultant reflexly induced EMG burst) occurs relatively earlier during the stretch phase in large- as compared with small-amplitude movements. Therefore the timing of the reflex muscle contraction is such that it would then be 'out of phase' with larger-amplitude movements and tend to damp rather than reinforce them.

Matthews (1972) comments concerning physiological tremor appear entirely accurate when transposed to a discussion of enhanced physiological tremor: 'If the spindle primaries are involved in the genesis of tremor it seems almost inevitable that as the whole system tends to oscillatory behaviour, the movement will in the first instance be restricted to the range in which the gain of the primary endings is greatest'. Our studies confirm this hypothesis—the amplitude of enhanced physiological tremor appears to be set by the small range of length changes over which the high sensitivity of primary spindle endings to very small stretches exists. This tremor, therefore, may be considered a by-product of the operational stretch servo.

Enhanced Physiological Tremor Compared to Voluntary Alternating Movements, Tremor-at-rest of Parkinson's Disease and Clonus

It should be noted that both in the enhanced tremors and in the responses to passive oscillatory movements there were pauses in afferent activity between the stretch discharges. There were no bursts of spindle activity during the contraction phases such as are seen during voluntary alternating tremor-like movements (fig. 5), where alpha and gamma motoneurons are co-activated during each contraction phase (Hagbarth, Wallin and Löfstedt, 1975). This agrees with the notion that in enhanced physiological tremor the rhythmical spindle inflow operates as a modulator of the alpha but not the gamma motoneurons in the firing motoneuron pool. Previous studies in man also indicate that with tendon jerks and tonic vibration reflexes the excitatory spindle inflow operates primarily on alpha-motoneurons, so that the resultant muscle contractions tend to unload the spindles (Burg *et al.*, 1973; Hagbarth, Wallin, Löfstedt and Aquilonius, 1975; Burke *et al.*, 1976). It should be noted, however, that in a recording such as that illustrated in fig. 5C, the rhythmical voluntary EMG contractions are timed to the movement cycles in a way similar to the EMG bursts in tremor (compare fig. 2). It seems likely that the segmental stretch reflex also plays some role in producing proper timing of the motor discharges in fast voluntary alternating movements, and this may explain the clinical maxim that it is not possible for a person to make a voluntary alternating movement at a rate greater than that of his existing tremor (whether it be physiological or a slower, pathological tremor) (Jung, 1941).

In the tremor-at-rest of Parkinson's disease, the oscillatory movements are most probably maintained, as are normal voluntary alternating movements, by rhythmical volleys in descending motor pathways of supraspinal origin which operate upon both alpha and gamma motoneurons (Hagbarth, Wallin and Löfstedt, 1975; Hagbarth, Wallin, Löfstedt and Aquilonius, 1975). Tremor-at-rest persists after dorsal rhizotomy, whereas in enhanced physiological tremors the oscillatory movements are more dependent on feed-back from the muscle. In summary, we believe that in the enhanced physiological tremors it is mainly the skeletomotor—not the fusimotor—output that oscillates whereas in voluntary alternating movements and the tremor-at-rest of Parkinson's disease, the oscillations involve both motor systems.

A major difference between enhanced physiological tremor and clonus may be that in the former type of oscillatory movement the stretch reflex merely affects the timing of discharges in an already-firing motoneuron pool, whereas in the latter the spindle stretch discharges are the main generators of the rhythmical skeletomotor outflow (compare Hagbarth, Wallin, Löfstedt and Aquilonius, 1975; Szumski *et al.*, 1974). It also appears that in patients with clonus the stretch reflex has lost its normal dual ability to act not only as a driving force for low-amplitude tremulous movements, but also as a force which damps the larger oscillations initiated by brisk perturbations of the contracting muscle.

That physiological tremors (with or without EMG grouping) are to be regarded as phenomena subserving some physiological purpose is debatable. In practical applications of System Control Theory, a rapid low-amplitude alternating movement (dither) is often added to a position servo to permit graded or proportional control of non-linear or discontinuous systems. Whether physiological tremor can serve a similar purpose for the motor control of body parts remains to be demonstrated.

SUMMARY

Microneurographic studies were made of normal human muscle spindle afferent activity to evaluate the role played by these endings, and by the segmental stretch reflex, in various types of physiological tremor. Primary endings are sufficiently sensitive to respond to the minute tremulous movements normally seen in contracting muscles. Human muscle spindle endings appear to possess the same non-linear sensitivity to small stretches as has been reported for cat muscle spindles.

The findings also support the notion that the segmental stretch reflex plays an important role in enhanced physiological tremor, in so far as it tends to synchronize the motor outflow in such a way as to produce rhythmical contractions properly timed to reinforce the mechanical resonant properties of the moving parts. At the same time, because of the non-linear properties of muscle spindle endings, the stretch reflex also serves to damp the larger oscillations of finger or hand which result from a brisk tap or muscle twitch. There is no evidence for alpha-gamma co-activation in these enhanced physiological tremors.

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REFERENCES

ALLUM, J. H. J., DIETZ, V. and FREUND, H.-J. (1978) Neuronal mechanisms underlying physiological tremor. *Journal of Neurophysiology*, **41**, 557–571.

BERTHOZ, A. and METRAL, S. (1970) Behaviour of a muscular group subjected to a sinusoidal and trapezoidal variation of force. *Journal of Applied Physiology*, **29**, 378–384.

BINDER, M. D. and STUART, D. G. (1979) Motor unit-muscle receptor interactions: design features of the neuromuscular control system. In: *Progress in Clinical Neurophysiology*. Vol. 8. *Motor Control in Man: Suprasegmental and Segmental Mechanisms*. Edited by J. E. Desmedt. Basel: Karger. In press.

BRUMLIK, J. and YAP, C. B. (1970) *Normal Tremor*. Springfield, Ill.: C. C. Thomas, pp. 51–75.

BURG, D., SZUMSKI, A. J., STRUPPLER, A. and VELHO, F. (1973) Afferent and efferent activation of human muscle receptors involved in reflex and voluntary contraction. *Experimental Neurology*, **41**, 754–768.

BURKE, D., HAGBARTH, K.-E. and LÖFSTEDT, L. (1978*a*) Muscle spindle responses in man to changes in load during accurate position maintenance. *Journal of Physiology, London*, **276**, 159–164.

—— —— —— (1978*b*) Muscle spindle activity in man during shortening and lengthening contractions. *Journal of Physiology, London*, **277**, 131–142.

—— —— —— and WALLIN, B. G. (1976) The responses of human muscle spindle endings to vibration during isometric contraction. *Journal of Physiology, London*, **261**, 695–711.

—— —— and WALLIN, B. G. (1979) Alpha-gamma linkage and the mechanisms of reflex reinforcement. In: *Progress in Clinical Neurophysiology*. Vol. 8. *Motor Control in Man: Suprasegmental and Segmental Mechanisms*. Edited by J. E. Desmedt. Basel: Karger. In press.

—— and SCHILLER, H. H. (1976) Discharge pattern of single motor units in the tonic vibration reflex of human triceps suræ. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 729–741.

—— SKUSE, J. F. and STUART, D. G. (1979) The regularity of muscle spindle discharge in man. *Journal of Physiology, London*, **291**, 277–290.

CRAGO, P. E., HOUK, J. C. and HASAN, Z. (1976) Regulatory actions of human stretch reflex. *Journal of Neurophysiology*, **39**, 925–935.

DESMEDT, J. E. and GODAUX, E. (1975) Vibration-induced discharge patterns of single motor units in the masseter muscle in man. *Journal of Physiology, London*, **253**, 429–442.

DIETZ, V., BISCHOFBERGER, E., WITA, C. and FREUND, H.-J. (1976) Correlation between the discharges of two simultaneously recorded motor units and physiological tremor. *Electroencephalography and Clinical Neurophysiology*, **40**, 97–105.

ELBLE, R. J. and RANDALL, J. E. (1976) Motor-unit activity responsible for 8- to 12-Hz component of human physiological finger tremor. *Journal of Neurophysiology*, **39**, 370–383.

EVARTS, E. V. and BIZZI, E. (1976) Some teleological considerations regarding myotatic reflexes. In: *Abstracts of Communications* at the International Symposium on Human Reflexes and Motor Disorders: Brussels, 21–23 April. Edited by J. E. Desmedt, Brain Res. Unit, 115 Bd. de Waterloo, B1000, Brussels, pp. 71–72.

—— and VAUGHN, W. J. (1978) Intended arm movements in response to externally produced arm displacements in man. In: *Progress in Clinical Neurophysiology*. Vol. 4. *Cerebral Motor Control in Man: Long Loop Mechanisms*. Edited by J. E. Desmedt. Basel: Karger, pp. 178–192.

FREUND, H.-J. and DIETZ, V. (1978) The relationship between physiological and pathological tremor. In: *Progress in Clinical Neurophysiology*. Vol. 5. *Physiological Tremor, Pathological Tremors and Clonus*. Edited by J. E. Desmedt. Basel: Karger, pp. 66–89.

GOODWIN, G. M., HULLIGER, M. and MATTHEWS, P. B. C. (1976) Studies on muscle spindle primary endings with sinusoidal stretching. In: *Progress in Brain Research*. Vol. 44. *Understanding the Stretch Reflex*. Edited by S. Homma. Amsterdam: Elsevier, pp. 89–98.

GRANIT, R. (1955) *Receptors and Sensory Perception*. New Haven: Yale University Press, pp. 191–236.

HAGBARTH, K.-E., HELLSING, G. and LÖFSTEDT, L. (1976) TVR and vibration-induced timing of motor impulses in the human jaw elevator muscles. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 719–728.

—— HONGELL, A., HALLIN, R. G. and TOREBJÖRK, H. E. (1970) Afferent impulses in median nerve fascicles evoked by tactile stimuli of the human hand. *Brain Research, Amsterdam*, **24**, 423–442.

—— and VALLBO, Å. B. (1978) Discharge characteristics of human afferents during muscle stretch and contraction. *Experimental Neurology*, **22**, 674–694.

—— WALLIN, G., BURKE, D. and LÖFSTEDT, L. (1975) Effects of the Jendrassik manœuvre on muscle spindle activity in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 1143–1153.

—— —— and LÖFSTEDT, L. (1975) Muscle spindle activity in man during voluntary fast alternating movements. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 625–635.

—— —— —— and AQUILONIUS, S.-M. (1975) Muscle spindle activity in alternating tremor of Parkinsonism and in clonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 636–641.

HALLIDAY, A. M. and REDFEARN, J. W. T. (1956) An analysis of the frequencies of finger tremor in healthy subjects. *Journal of Physiology, London*, **134**, 600–611.

HOMMA, S., KANDA, K. and WATANABE, S. (1972) Preferred spike intervals in the vibration reflex. *Japanese Journal of Physiology*, **22**, 421–432.

JUNG, R. (1941) Physiologische Untersuchungen über den Parkinson-Tremor und andere Zitterformen beim Menschen. *Zeitschrift für das gesamte Neurologie und Psychiatrie*, **173**, 263–332.

LANCE, J. W. and MCLEOD, J. G. (1975) *A Physiological Approach to Clinical Neurology*. London: Butterworths, pp. 127–128.

LEE, R. G. and TATTON, W. G. (1975) Motor responses to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. *Canadian Journal of Neurological Science*, **2**, 285–293.

LIPPOLD, O. C. J. (1970) Oscillation in the stretch reflex arc and the origin of the rhythmical, 8–12 c/s component of physiological tremor. *Journal of Physiology, London*, **206**, 359–382.

—— REDFEARN, J. W. T. and VUCO, J. (1957) The rhythmical activity of groups of motor units in the voluntary contraction of muscle. *Journal of Physiology, London*, **137**, 473–487.

MARSDEN, C. D. (1978) The mechanisms of physiological tremor and their significance for pathological tremors. In: *Progress in Clinical Neurophysiology*. Vol. 5. *Physiological Tremor, Pathological Tremors and Clonus*. Edited by J. E. Desmedt. Basel: Karger, pp. 1–16.

—— MERTON, P. A., MORTON, H. B., ADAM, J. E. R. and HALLETT, M. (1978) Automatic and voluntary responses to muscle stretch in man. In: *Progress in Clinical Neurophysiology*. Vol. 4. *Cerebral Motor Control in Man: Long Loop Mechanisms*. Edited by J. E. Desmedt. Basel: Karger, pp. 167–177.

MARSHALL, J. and WALSH, E. G. (1956) Physiological tremor. *Journal of Neurology, Neurosurgery and Psychiatry*, **19**, 260–267.

MATTHEWS, P. B. C. (1972) *Mammalian Muscle Receptors and Their Central Actions*. Baltimore: Williams and Wilkins, p. 580.

—— and STEIN, R. B. (1969) The sensitivity of muscle spindle afferents to small sinusoidal changes of length. *Journal of Physiology, London*, **250**, 723–743.

NEILSON, P. D. and NEILSON, M. D. (1978) The role of action reflexes in the damping of mechanical oscillations. *Brain Research, Amsterdam*, **142**, 439–453.

POPPELE, R. E. and BOWMAN, R. J. (1970) Quantitative description of linear behaviour of mammalian muscle spindles. *Journal of Neurophysiology*, **33**, 59–72.

SHAHANI, B. T. and YOUNG, R. R. (1973) Studies of the normal human silent period. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, pp. 589–602.

—— —— (1976) Physiological and pharmacological aids in the differential diagnosis of tremor. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 772–783.

—— —— (1978) Action tremors: a clinical neurophysiological review. In: *Progress in Clinical Neurophysiology*. Vol. 5. *Physiological Tremor, Pathological Tremors and Clonus*. Edited by J. E. Desmedt. Basel: Karger, pp. 129–137.

SOMMER, J. (1941) Synchronisierung motorisher Impulse und ihre Bedeutung für die Neurophysiologische Forschung. *Zeitschrift für das Gesamte Neurologie und Psychiatrie*, **172**, 500–530.

STRUPPLER, A., BURG, D. and ERBEL, F. (1973) The unloading reflex under normal and pathological conditions in man. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, pp. 603–617.

—— and ERBEL, F. (1971) Analysis of proprioceptive excitability with special reference to the 'unloading reflex'. In: *Neurophysiology Studied in Man*. Edited by G. G. Somjen. Amsterdam: Excerpta Medica. Vol. 253, pp. 298–304.

SZUMSKI, A. J., BURG, D., STRUPPLER, A. and VELHO, F. (1974) Activity of muscle spindles during muscle twitch and clonus in normal and spastic human subjects. *Electroencephalography and Clinical Neurophysiology*, **37**, 589-597.

VALLBO, Å. B. (1970) Discharge patterns in human muscle spindle afferents during isometric voluntary contractions. *Acta Physiologica Scandinavica*, **80**, 552-566.

—— (1973*a*) Muscle spindle afferent discharge from resting and contracting muscles in normal subjects. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, pp. 317-324.

—— (1973*b*) Impulse activity from human muscle spindles during voluntary contraction. In: *Motor Control*. Edited by A. A. Gydikov, N. T. Tankov and D. S. Kosarov. New York: Plenum Press, pp. 33-43.

—— HAGBARTH, K.-E., TOREBJÖRK, H. E. and WALLIN, B. G. (1979) Proprioceptive, somatosensory and sympathetic activity in peripheral human nerves. *Physiological Reviews*, **59**. In press.

VILIS, R. and COOKE, J. D. (1976) Modulation of the functional stretch reflex by the segmental reflex pathway. *Experimental Brain Research*, **25**, 247-254.

YOUNG, R. R. and HAGBARTH, K.-E. (1980) Physiological tremor enhanced by manœuvres affecting the segmental stretch reflex. In preparation.

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Brain (1979), **102**, 527-558

DOWNWARD GAZE IN MONKEYS

STIMULATION AND LESION STUDIES

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INTRODUCTION

THE location of the oculomotor pathways within the monkey brain has been partly delineated physiologically by means of stimulation and ablation experiments (for reviews *see* Schäfer, 1900; Pasik and Pasik, 1975). It appears that horizontal conjugate eye movements to one side are widely represented over the cortex of the contralateral cerebral hemisphere, and the functional pathway descends in a convergent fashion through the subthalamic region to the mesencephalic reticular formation. A crossing occurs at the level of the oculomotor and trochlear nerve nuclei (oculomotor decussation for horizontal gaze). More caudally, the pathway can be identified within the paramedian zone of the pontine reticular formation (PPRF) down to the level of the abducens nerve nucleus. There is recent anatomical and electrophysiological evidence that this pathway activates two types of neurons within the latter nucleus: motoneurons, which innervate the lateral rectus, and internuclear neurons, whose axons project across the midline, ascend in the opposite medial longitudinal fasciculus and reach the oculomotor nucleus where they activate the motoneurons for the medial rectus, thus providing the mechanisms for conjugate gaze (Carpenter, McMasters and Hanna, 1963; Graybiel and Hartweig, 1974; Baker and Highstein, 1975; Büttner-Ennever and Henn, 1976). Such general outline is all compatible with clinicopathological observations in man showing that defects in horizontal conjugate gaze contralateral or ipsilateral to the lesion follow damage rostral or caudal to the decussation of the pathways, respectively, and that the extent of the destruction necessary to produce a given oculomotor deficit is considerably larger at the cerebral than at the pontine level.

The mechanisms for vertical gaze are less clearly understood. The myth that the superior colliculi contain 'centres' for vertical gaze and for 'automatic' eye movements (Whitteridge, 1960) has been conclusively dispelled by ablation experiments in monkeys (Pasik, Pasik and Bender, 1966). After the immediate post-operative period, these animals could move the eyes in every direction and the evoked optokinetic and vestibular nystagmus could be elicited in both the horizontal and vertical planes. Based on clinical and experimental data, it has been proposed that vertical eye movements are mediated by *bilateral* activation of the same pathways which subserve conjugate horizontal deviations to the right and to the left (Bender, 1960). Gaze disturbances in the vertical plane would result from *bilateral* damage to 'critical structures'. Indeed, bilateral simultaneous stimulation of the cerebral cortex results in true vertical movements which are rarely elicited on unilateral stimulation (Mott and Schäfer, 1890; Pasik and Pasik 1964); bilateral caloric irrigation of the ear canals elicits vertical nystagmus (Shanzer and Bender, 1959); adequate visual input to *both* cerebral hemispheres is a prerequisite for normal optokinetic nystagmus in the strict vertical plane (Pasik, Pasik, Valciukas and Bender, 1971). As a counterpart, lesions across the right and left side of the paramedian pontine reticular formation not only cause paralysis of gaze to the right and to the left, but also of vertical gaze (Bender and Shanzer, 1964). The search for a critical region for vertical upward eye movements, that is, a zone, the destruction of which will interfere with this function without affecting horizontal gaze, met with success in 1969. It was found that monkeys with bilateral lesions of the pretectum including the interstitial nuclei of the posterior commissure, or with median section of this commissure, exhibited paralysis of upward movements of the eyes accompanied by retraction of the eyelids and pupillary disturbances (Pasik, Pasik and Bender, 1969*a*; Pasik and Pasik, 1975). Moreover, upward nystagmus evoked by either optokinetic or bilateral vestibular stimulations was abolished and in many instances replaced by binocular adductive saccades (Pasik, Pasik and Bender, 1969*b*). Some of these monkeys had additional impairment of downward gaze but in no instance was there an isolated paralysis of downward movement. From the foregoing, it was concluded that the posterior commissure and its nuclei were directly concerned with the mechanisms for upward gaze. The 'pretectal syndrome' or 'syndrome of lesion of the posterior commissure' as summarized above has been observed with relative frequency in the clinic. A recent clinicopathological study from this Department, which included 15 patients with isolated paralysis of upward gaze, revealed that they all had either bilateral lesions involving the pretectum or unilateral damage destroying the adjacent posterior commissure (Christoff, 1974).

Critical regions for downward eye movements have been more elusive. An isolated paralysis of downward gaze had not been produced experimentally and, to our knowledge, only five clinical cases with post-mortem pathological examination have been reported thus far (Schuster, 1921 and Muskens, 1934; André-Thomas, Schaeffer and Bertrand, 1933; Jacobs, Anderson and Bender, 1973; Cogan, 1974; Halmagyi, Evans and Hallinan, 1978). All these patients had had more or less symmetrical bilateral vascular lesions which involved parts of the medial and ventral regions of the thalamus, the subthalamic area rostral to and in between the red nuclei impinging on the central grey matter and the oral pole of the oculomotor nerve complex. Some of these reports have emphasized the possible importance of the fasciculus retroflexus since this structure was destroyed bilaterally in most of the instances (Jacobs *et al.*, 1973; Halmagyi *et al.*, 1978). These clinicopathological findings served as cues for the present investigation of specific areas critically concerned with downward gaze. Since previous experiments indicated that extensive bilateral destruction of the medial thalamus did not interfere with eye movements in any direction (Pasik *et al.*, 1969*a*), the search was concentrated in the subthalamic and rostral midbrain regions. Preliminary reports on this work have been presented earlier (Kömpf, Pasik and Pasik, 1977).

MATERIAL AND METHODS

Subjects

Ten monkeys (*Macaca mulatta*), weighing 2.5–5 kg, were studied before and after circumscribed lesions placed in the mesodiencephalic junction.

Testing and Recording Procedures

In addition to complete neurological examination, special care was taken in the evaluation of the following tests of oculomotor functions before and after making the lesions: (*a*) spontaneous and pursuit eye movements examined by direct inspection; (*b*) oculocephalic reflexes, elicited by turning of the head to either side, and up and down, which normally produces a conjugate deviation of the eyes to the side opposite to the direction of the turning; (*c*) pupillary reflexes to ordinary flashlight stimulation; (*d*) optokinetic nystagmus (OKN) and after-nystagmus (OKAN) in the horizontal, vertical and oblique (45 degrees) planes tested according to techniques described in detail in previous publications (Pasik *et al.*, 1969*b*; Pasik *et al.*, 1971). Each monkey was placed in a primate chair, with the limbs restrained and the head fixed by a custom-fitted helmet, behind a rear-projection screen which covered about 135 degrees of the visual field. A film-loop projector was used to produce 4 luminous stripes, 2.5 cm wide, separated by 27.5 cm dark intervals, which moved at constant speed resulting in a frequency of 2 Hz. The loop-transport mechanism could be tilted so as to present vertical stripes which moved to the right or to the left, horizontal stripes with up and down displacement, and stripes inclined 45 degrees with oblique movements from right and down to left and up (RD→LU) and vice versa, or from left and down to right and up (LD→RU) or vice versa. The testing started thirty minutes after intramuscular injection of 1 mg/kg body weight of amphetamine sulphate which helped to maintain a stable level of alertness; (*e*) vestibular nystagmus elicited by caloric or rotatory stimulation in the light as well as in short periods of darkness. Caloric tests were performed by irrigating one ear at the time, or both ears simultaneously, with 50 ml of cold (5° C) or warm (48° C) water for about 50 s with the monkey in the erect position. Turning tests consisted of fourteen turns of a manually-driven bench in about 30 s with the animal in the erect or right lateral position, observations being made during rotation and after sudden stop.

The eye movements elicited by optokinetic and vestibular stimulation were electrically recorded through platinum needle electrodes inserted subcutaneously at the four cardinal points of each periorbital region. Electrode pairs (vertical or horizontal, for the right or left eye) were connected to one of four polygraph channels with RC amplification. The method which has been described in detail in previous publications (Pasik *et al.*, 1971; Pasik, Valciukas and Pasik, 1973) allowed the identification of eight vectors of rapid eye movements with respect to the head namely upward, downward, to the right, to the left, and the four intermediate obliques.

Stimulation, Lesions and Histological Procedures

A stereotaxic instrument was used to direct bipolar coaxial electrodes vertically under light sodium pentobarbital anæsthesia and sterile precautions. The stereotaxic AP plane was corrected for individual monkeys, by taking skull x-rays in perfectly aligned lateral projection which was made possible by placing a minute lead pellet in each ear canal and making them superimpose under fluoroscopy. The horizontal plane was determined on rœntgenograms by a line connecting the infraorbital ridge and the dense image of the pellet. If the distance between the anterior clinoid process and the perpendicular line through the pellet was 18 mm, no correction was necessary. If it was greater, the difference with 18 was added to the frontal planes of the atlas (Olszewski, 1952). The electrode shaft, 0.5 mm in outside diameter, was insulated except for 0.5 mm at the tip and connected to the negative side of the stimulator. The centre lead, which was connected to the positive side, protruded 1 mm from the shaft and only the extreme 0.5 mm was uninsulated. One to three such electrodes were introduced symmetrically on each side and moved at 1 mm intervals. The stimuli were produced by a Grass Model S8 stimulator and consisted of 1-3 s trains of 0.5 ms square pulses at a frequency of 250 Hz. Each point was stimulated at least twice to make certain that the response was reproducible, the interval between stimulations being longer than 1 min.

Responses were noted by at least two observers and occasionally were filmed. Stimulation was made bilaterally and simultaneously at all electrode locations. Unilateral (right and left) stimulation was also delivered at points where bilateral stimuli evoked an eye movement response other than eye centring. Voltages varied from 3 to 12 volts. All stimulus parameters were frequently monitored on a 2-channel CR oscilloscope. One or two AP planes were explored in each animal with locations between A+5.5 and A+14.0. In one of the monkeys (No. 858) this was made in two separate experiments, thirty days apart. At the end of the stimulation session, bilateral or unilateral electrolytic lesions were made, centred at the locations from which the strongest downward eye movements had been elicited. For this purpose, the coaxial electrode was shorted and connected to the anode of a DC source. The cathode was a large copper strip wrapped around the abdomen. A total of 5 mA of current was passed for 20–45 s. Occasionally, stimuli were also delivered at the same and other locations in the electrode track after the lesion was made.

Post-operative testing was carried out daily and then weekly until reaching either complete recovery or a plateau of improvement of at least four weeks. Monkeys were killed at least three months after the lesion by perfusion through the aorta under deep barbiturate narcosis with saline solution followed by 5 per cent formalin. The brain was removed and a block containing the electrode tracks was embedded in celloidin and cut serially at 40 μm. One in every ten sections were stained with the Klüver-Barrera method and used to reconstruct the location and extent of the lesions, as well as to determine the actual position of the electrode tracks. The results which follow are given in terms of those corrected values with due consideration for the shrinkage produced during the histological processing and therefore reflect the dimensions in the living state.

RESULTS

Effects of Electrical Stimulation

The tracks explored in the 10 monkeys extended over almost every cubic millimetre of tissue situated between the AP planes +11.5 (tuberal region of the hypothalamus), and +5.0 (rostral midbrain containing the oral pole of the III nerve nucleus), laterally 0.5 to 6 mm from the midline, and from the thalamus to the III nerve rootlets in the H plane. In other words, most of the diencephalon (thalamus, hypothalamus, subthalamus and epithalamus) as well as the rostral midbrain was stimulated within 6 mm from the midline both unilaterally and bilaterally. In addition, the A+14.0 plane was explored, as well as some regions between 6 and 8 mm from the midline. The predominant response to a bilateral simultaneous electrical stimulation in the anesthetized monkey was a binocular downward movement usually associated with pupillary dilation (fig. 1). As a rule,

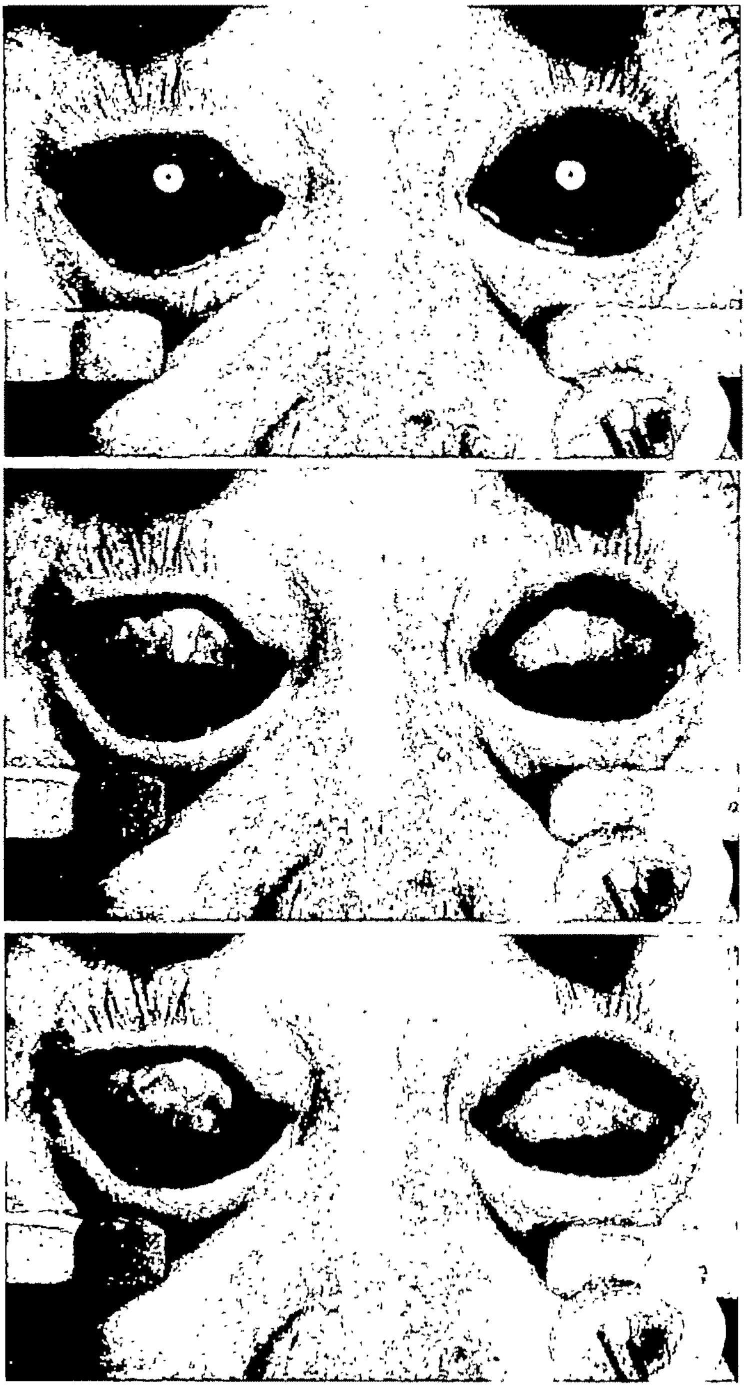
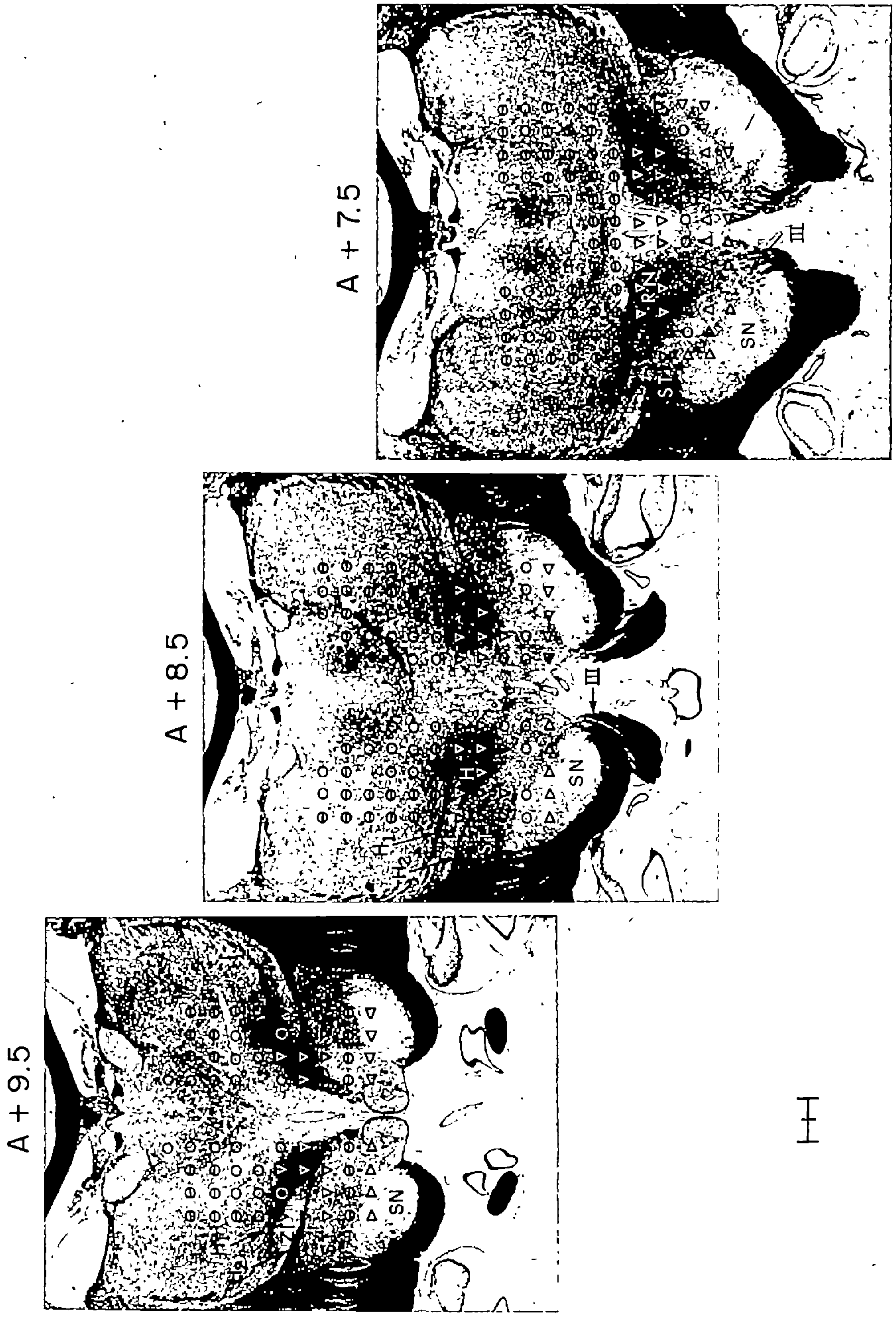


FIG. 1. Bilateral simultaneous stimulation of the mesodiencephalic junction. Frames from 16 mm moving picture film. Upper eyelids are held opened by gentle retraction. Glow along left bar in neon bulb at lower right indicates stimulus on. *Top*, before stimulation. *Centre*, 600 ms after stimulus onset. *Lower*, 600 ms later. Note the strong straight downward deviation of the eyes elicited by the stimuli.


A + 7.5
RN
SN
STN
III
A + 8.5
H
H1
H2
STN
SN
III
A + 9.5
SN
H1
H2

the sequence of responses in the dorsoventral progression of the electrodes followed a similar pattern in most tracks. The initial reactions at the level of the thalamus were a slight dilation of the pupils and eye centring movements, that is each eye moved to the mid-position, regardless of their prestimulus location. At deeper levels, that is, in the subthalamic region, binocular downward movements appeared (fig. 1). Further, in the rostral midbrain including the red nucleus and substantia nigra, only bilateral pupillary dilation was evoked. Ultimately, there was a brisk monocular or binocular adduction movement. The electrodes were not advanced beyond the points giving the latter response. This pattern of reactions which appear concentrated from A+10 to A+7, and between 1 and 6 mm from the midline, is illustrated in fig. 2 for three selected planes.

All stimulations were conducted under varying depths of pentobarbital anæsthesia and the level of narcosis was an important determinant of the magnitude of the response. Under deep anæsthesia, no eye movements could be elicited. Binocular deviations appeared only if sufficient time were allowed for the narcosis to lighten. All vertical movements were lost in one of the animals when the general physical state deteriorated during the experiment. It is noteworthy that downward deviations did occur, however, under levels of anæsthesia, which resulted in pupillary constriction, loss of corneal reflexes and lack of reaction to painful stimuli. The stimulus thresholds varied with the level of anæsthesia in a predictable manner. When suprathreshold values were used there was never a change in the quality of response, but sometimes stronger and longer lasting deviations were obtained which occasionally outlasted the stimulus. No differences in threshold were observed for responses evoked from more medially as opposed to more laterally placed electrodes. Although the intensity of the utilized stimulus varied among animals, it was quite constant within a preparation so that there was no particularly sensitive zone within the region from where straight downward deviation of the eyes could be elicited.

Conjugate downward deviation of the eyes. Bilateral simultaneous stimulation elicited reliable binocular downward movements from a relatively large zone. As determined in 7 monkeys, this region was located between the A planes +10 and +7, up to 5–6 mm from the midline, and only 2–3 mm in the H plane, with the centre about 3 mm above the level yielding monocular or binocular adduction. This area contains the subthalamus and part of the rostral midbrain tegmentum.

FIG. 2. Pattern of responses to bilateral simultaneous stimulation in stereotaxic planes containing the critical region for downward eye movements. Deviations downward and upward, always accompanied by pupillary dilation, are represented by ▽, △, respectively, inward movements by ▷ ◁, pupillary dilation or eye centring by ○ and — respectively; both of these reactions by ⊖. H, H_1, H_2, fields of Forel; ST, subthalamic nucleus; SN, substantia nigra; III, third nerve rootlets; RN, red nucleus. Note the concentration of responses downward in the subthalamic region and rostral midbrain. The active points are consistently found 2–3 mm above the III nerve rootlet reaction (strong inward movement of one or both eyes). In the most caudal plane (A+7.5) reliable responses upward occurred 1–2 mm ventral to the points giving downward movements. Full scale: 2 mm.

Prominent structures within this zone include the fields of Forel, zona incerta, subthalamic nucleus, oral pole of the red nucleus, fasciculus retroflexus, and more vaguely defined cell groups in the so-called area tegmentalis. The downward eye movements had occasionally a slight oblique component to either side or a minimal binocular adductive or convergent quality. The binocular downward responses were always accompanied by pupillary dilation and sometimes preceded by eye centring. The downward deviation was goal-directed, that is, regardless of the position of the eyes prior to stimulation, the final position was always far below the horizontal meridian. The binocular deviations were usually smooth and equal in the two eyes, and the amplitude was such that the cornea became partially and sometimes almost totally covered by the lower eyelid. Although these responses were obtained in general by stimulation of homotopic points (+0.5 mm) on both sides of the midline, similar results derived from asymmetric placements of up to 2 mm within the reactive zone.

Unilateral stimulation of the same region outlined above gave a variety of results. From a total of 46 locations where bilateral stimulation yielded downward binocular deviations, unilateral stimulation elicited oculomotor activity from only 63 per cent of the points. These responses were straight downward (26 per cent), oblique downward and contralateral (15 per cent), convergent downward (7 per cent), downward with strong rotatory component (4 per cent), or centring of the eyes (11 per cent). There were no purely horizontal contralateral or ipsilateral conjugate movements. In addition there was bilateral pupillary dilation which occasionally represented the entire response (22 per cent). Finally no reaction whatsoever was obtained from 15 per cent of the locations. The latter points were mostly in the areas away from the midline whereas eye centring occurred more frequently on stimulation of more medial locations. Downward deviations failed to occur on unilateral stimulation of points from which bilateral stimulation yielded only weak downward movements of brief duration.

Conjugate upward deviation of the eyes. Bilateral simultaneous stimulation elicited conjugate eye movements upwards only from the A+7.5 plane, which was explored in 4 monkeys. The active points for this response were located 1–2 mm ventral and medial to the area evoking downward movements, and 1 mm dorsal to the region giving adductive responses (fig. 2). Anatomically, the points yielding upward movements were located ventral and medial to the red nucleus. The binocular movements were straight upward in two of the animals and slightly oblique to right or left in the other two. Upward deviations were never as strong as the downward movements elicited from more dorsal locations in the same tracks. *Unilateral stimulation* resulted in either oblique movements in an upward and contralateral direction, or in an upward deviation with a strong torsional component.

Other ocular, pupillary and body movements. Eye centring was very common and could be observed from almost all points stimulated bilaterally, that is not only from the region yielding vertical eye movements but also from areas lying 4 mm rostrally, and 2 mm caudally to it. This response also resulted from stimulation of points within 6–7 mm dorsal to critical loci for vertical eye movements and, therefore, included almost the entire thalamus from its oral pole to the level of the centromedian-parafascicular complex. The eye centring phenomenon was often associated with pupillary dilation (*see below*) and frequently preceded a conjugate vertical deviation when the proper region was stimulated. Occasionally, eye centring also occurred on unilateral stimulation (11 per cent of stimulated points). Convergent movements accompanied the downward deviations in 20 per cent of the instances whereas rotatory components were only rarely observed. On three occasions there were also associated nystagmoid jerks which were downward in one and upward in the other two instances. On several instances, the binocular movements were not perfectly conjugate, so that the amplitude was different for each eye.

Bilateral pupillary dilation was a very common response within and without the critical zone eliciting vertical eye movements. Outside this region, it was usually accompanied by eye centring but contrary to the latter response, it was also commonly evoked by unilateral stimulation (74 per cent of the cases). Occasionally, dilation was unequal. Pupillary constriction was observed only from very rostral locations within the anterior and medial hypothalamus. Movements of the face, jaw and upper limbs, as well as vocalization were elicited on occasions, particularly from the thalamus and only rarely from the zone which yielded binocular movements.

Effects of stimulation after lesions. After bilateral electrolytic lesions were made at the points yielding maximal downward eye deviations, repeated bilateral stimulation of the same points resulted in strong binocular adduction and pupillary dilation. In general, downward movements could no longer be elicited. In two animals where downward deviations could still be obtained, additional enlargements of the electrolytic lesions resulted in complete abolition of the downward response to subsequent electric stimuli. In a third monkey, (No. 858), considerably extensive lesions in the A+8 plane failed to eliminate the downward response on repeated stimulation.

Effects of Bilateral Lesions

Anatomical observations. Table 1 gives the extent and location of the lesions in individual animals. This section concerns the findings in the first 7 monkeys listed, where lesions were made bilaterally. In all but one (No. 868) the most extensive electrolytic damage was centred about 2 mm from the midline in the subthalamic and rostral midbrain regions approximately in the A+8 plane. The rostrocaudal extent varied from 5 to 6 mm in Nos. 842, 858, 859 to 2 to 3 mm in Nos. 840, 857 (fig. 3). The actual volume of the minimal lesion was calculated from serial sections in Monkey 857 and found to be 2.375 mm^3 on the right and 2.806 mm^3 on the left.

TABLE 1. EXTENT OF THE LESIONS PER INDIVIDUAL ANIMAL

Monkey No.	*Extent of lesions in 'A' stereotaxic plane*		*Prerubral field*	*H_1 field of Forel*	*H_2 field of Forel*	*Red nucleus (oral pole)*	*Zona incerta*	*Subthalamic nucleus*	*Substantia nigra (lesion)*	*Substantia nigra (degeneration of pars compacta)*	*Fasciculus retroflexus*	*Ventral thalamic nuclei*	*Medial thalamic nuclei*	*Anterior thalamic nuclei*	*Intralaminar nuclei*	*N. of Darkschewitsch*	*N. of Cajal*	*Hypothalamus*	*Internal capsule*	*Pallidum*
	Maximal	*Rostro caudal*																		
840	7.5	8.5/6.5	X	l	l	L	l				L	Rl	l		X	L	L			
842	8.5	11.5/6.5	X			x					X	x	x							
855	7.5	10.5/6.5	X			l					X	X	x							
857	8.0	9.5/6.5	X	R	R	x				r										
858	8.5	12.5/7.0	X	X	X	lR	X	Lr	l	X		Lr	r	l				x		
859	8.5	12 5/6.5	X	l	l	l	l	Lr	r	X		X	x							
868	10.5	12.5/9.5						R	r	R		l						L	lR	
860	8.5	11.5/5.5	l	L	L	l	L	L		l		L								
870	10.5	11.5/9.5			R					R		r						r	R	r
872	10.0	11.5/7.5	L		L	l		l	l	l								l	l	

X, R and L = marked bilateral, right or left involvement. x, r and l = minimal bilateral, right or left damage. Monkey 858: two lesions centred at A + 10.5 and + 8.5. The extent of only the latter is given in the 2nd and 3rd column. Monkeys 842, 855, 859: thalamic damages include bilateral infarcts involving mainly n. ventralis anterior and partly n. ventralis lateralis, paracentralis and medialis dorsalis.

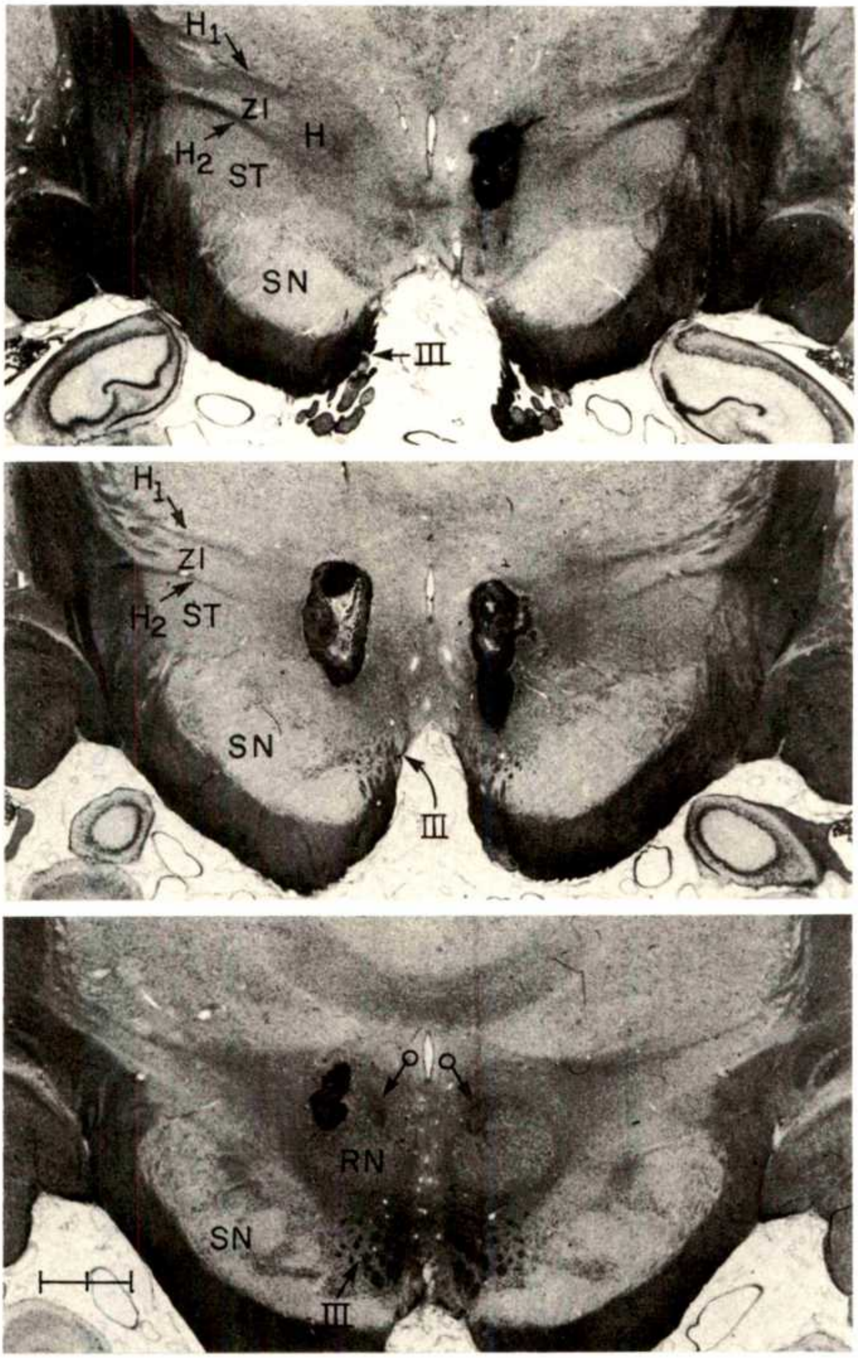


FIG. 3. Minimal bilateral lesions causing impairment of downward gaze. Notation as in fig. 2. Rapid downward eye movements were still impaired at the end of the three-month follow-up period. There is bilateral destruction of the prerubral fields and minimal involvement of the oral pole of the red nuclei. The fasciculus retroflexus is intact on both sides (ringed arrows). Klüver-Barrera stain. Full scale: 2 mm.

These values include a correction for shrinkage and are equivalent to spheres of about 1.7 mm in diameter. The lesions in Monkey 868 were located 2–3 mm more rostrally and only barely touched the most oral portion of the critical region to be described below. In the other 6 monkeys of this group, there was bilateral involvement of the prerubral fields. The H_1 and H_2 fields of Forel were not consistently affected and in some cases they were free of damage (Monkeys 842, 855). The lesions extended minimally into the oral pole of both red nuclei in Monkeys 842, 857, 858 and only on the left side in the other monkeys. The fasciculus retroflexus was free of damage in all but 3 of the monkeys. The interstitial nucleus of Cajal and the nucleus of Darkschewitsch were intact except in Monkey 842, where both of these nuclei were destroyed on the left side. The substantia nigra was minimally damaged on one side only in 3 of the animals. The pars compacta, however, showed marked retrograde changes in the monkeys with more extensive lesions and in Monkey 859 the degeneration was total and bilateral. Fig. 4 illustrates in a parasagittal section, 2 mm from the midline, the maximal and minimal extent of the lesions. It is apparent that the critical area is less than 2 mm in diameter and is located rostral and dorsal to the oral pole of the red nucleus.

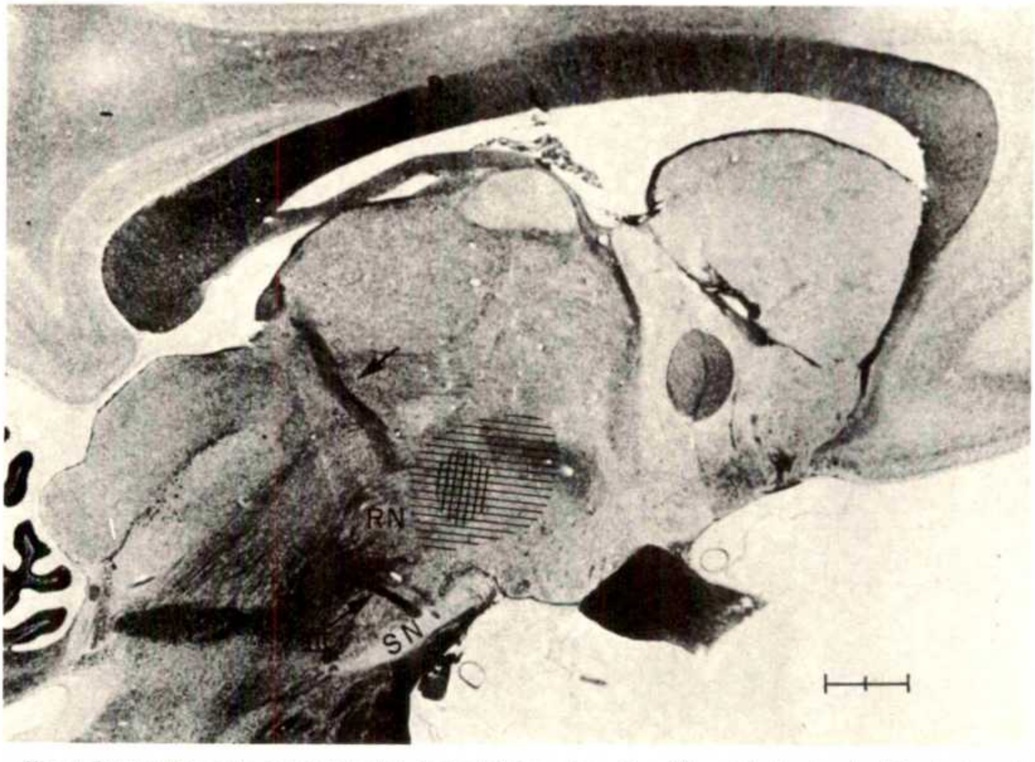


FIG. 4. Paramedian section of the monkey brain at 2.5 mm from the midline. Maximal and minimal extent of damage causing an impairment in downward gaze indicated by hatching and cross hatching respectively. Notation as in fig. 2. Note that the minimal lesion is located rostrally and dorsally to the red nucleus and that it spares the fasciculus retroflexus (arrows). Klüver-Barrera stain. Full scale: 2 mm.

Variously named cellular groups in this region, such as the nucleus of the prerubral field (Papez, 1942) and the rostral interstitial nucleus of the medial longitudinal fasciculus (Krieg, 1948; Büttner-Ennever and Büttner, 1978) appear to be involved in the lesions, which in any case include also the fibre systems coursing through the region. The entire district is classically known as the prerubral field and this uncommitted designation will be used to deal with our critical lesion. In addition to the electrolytic lesions, 3 of these monkeys (Nos. 842, 855, 859) showed a widespread bilateral symmetrical infarction involving mainly the thalamic nuclei ventralis anterior and to a lesser extent ventralis lateralis, paracentralis and medialis dorsalis.

Behavioural observations. Table 2 lists the disturbances in spontaneous and evoked eye movements as well as other motor and postural abnormalities observed in the 7 monkeys with bilateral lesions. It is readily apparent that only 6 of these animals showed marked deficits. The seventh monkey in the group (No. 868) exhibited only a slight limitation of downward gaze lasting three days. It should be recalled that its lesion did not involve the critical area (*see above*) and it will not be considered further.

Downward gaze. Conjugate eye movements downwards were initially impaired in all of the monkeys with bilateral lesions. Both spontaneous deviations as well as pursuit of targets were affected. The severity and duration of the deficit varied over the group. Spontaneous saccades downward were absent in all 6 monkeys for one to nine weeks. Thereafter, limited excursions were present, the eyes only slightly passing the horizontal meridian in some animals. Pursuit movements downward were less severely defective. In one monkey (No. 857), some following was present in the immediate post-operative period but it never recovered fully. In all the other animals, pursuit was absent for one to four weeks. It then reappeared and improved steadily reaching normal range one to three weeks later. It should be noted that two sets of lesions were made in Monkey 858, with a thirty-day interval. The first lesion, centred about the A+10.5 plane caused no deficits in eye movements, whereas the findings described above were present after the second set of lesions which were located 2 mm more caudally.

Upward Gaze. Conjugate eye movements upward showed a certain degree of deficit in 5 of the monkeys with bilateral lesions, the sixth animal (No. 857) having no such disturbances. The impairments were as a rule less severe and lasted a shorter period than those of downward gaze. For instance, in only 2 of the animals (Nos. 840, 842) was there an absence of upward deviations lasting six and nine days, respectively. In most cases, upward gaze was only limited in range and full pursuit movements recovered earlier than those in the downward direction.

Horizontal gaze. All the monkeys with bilateral lesions had consistently normal spontaneous and induced eye movements in the horizontal plane except for

TABLE 2. OCULOMOTOR AND POSTURAL DISTURBANCES PER INDIVIDUAL ANIMAL

Monkey No.	*Weight in kg*	*Survival in days*	*Downward gaze impairment*	*Upward gaze impairment*	*Preference of gaze*	*Oculocephalic reflexes and Bell's phenomenon*	*OKN downward*	*OKAN downward*	*OKN oblique downward*	*OKAN oblique downward*	*OKN upward*	*OKAN upward*	*OKN oblique upward*	*OKAN oblique upward*	*Vestibular nystagmus downward*	*Vestibular nystagmus upward*	*Pupillary disturbances*	*Head flexion*	*Limb paresis*
840	5.0	86	X	X	L	n	X	X	x	x				x	X		L		R
842	5.0	94	X	X		n	X	X	X	X	X	X	X	X	X	X			
855	3.0	93	X	x		n	X	X	X	X	x	X	X	X	X	x		X	
857	3.0	93	X			n	x	X	x	x		x		x	X				
858	2.8	90	X	x		n	X	X	X	X	x	X		x	X	x			R
859	2.6	49	X	X		n	X	X	X	X	x	X		x	X			x	
868	2.5	42	x			n												x	R
860	2.5	9				n													
870	2.8	28			R	n													
872	2.6	13				n													

X = major defect; x = minor defect; n = normal; R = right; L = left. Note the lack of oculomotor impairment in the last 3 animals which had only unilateral lesions. Only a very transient deficit was present in Monkey 868 which had a bilateral lesion but rostral to the critical region (*see* Table 1).

Monkey 840 which kept the eyes deviated to the left in the first post-operative day. This animal showed a preference of gaze to the left for another four days and became normal thereafter.

Oculocephalic reflexes. Eye deviations in the opposite direction of passive head movements were preserved in all planes, including upward and downward, in all animals. This phenomenon was present even during periods of absent spontaneous and pursuit eye movements downward. It is of interest that in such instances the monkey hyperextended the head on its own when attempting to fixate an object placed in the lower quadrants of the visual fields. This manœuvre brought the eyes below the horizontal meridian.

Other ocular movements and pupillary reflexes. Convergence while fixating on near objects and Bell's phenomenon were present in all the animals. There were no episodes of spontaneous or gaze-induced nystagmus. It is noteworthy that there were no signs of the pretectal syndrome such as binocular adductive or lightning eye movements, nor eyelid retraction (Pasik *et al.*, 1969*a*, 1969*b*; Pasik and Pasik, 1975). The pupils reacted normally to light in all but one (No. 840) of the animals; in this monkey the left pupil was dilated, and constricted to light only weakly and slowly.

Optokinetic nystagmus. Pre-operatively, optokinetic nystagmus was elicited with normal characteristics in the horizontal, vertical (up and down) (fig. 5) and oblique directions (fig. 6) in all monkeys. The frequency of the response was about the same as the frequency of stimulation, namely, 2 Hz. In general, responses downward were more regular and of larger amplitude than those upward, an observation previously noted in normal monkeys (Pasik *et al.*, 1969*b*; Pasik *et al.*, 1971). In some of the animals, optokinetic nystagmus to the right or left exhibited a slight degree of obliquity upward or downward. Optokinetic nystagmus elicited by stimuli moving in the two 45 degrees directions also showed normal characteristics in 5 of the monkeys. Monkey 868 responded with optokinetic nystagmus only in the horizontal plane, and Monkey 855 was not tested pre-operatively. Optokinetic after-nystagmus occurred always in the same direction as the preceding optokinetic nystagmus when the latter was in the horizontal plane downward. Optokinetic nystagmus with straight or oblique upward components was followed in many instances by either no after response or an optokinetic after-nystagmus with downward components, as if cessation of the stimulus reversed the vertical vector.

After bilateral lesions, vertical and oblique optokinetic nystagmus and after-nystagmus were affected in all 6 animals (figs. 5, 6). Downward optokinetic nystagmus was initially absent in 5 monkeys (Nos. 840, 842, 855, 858 and 859) for a two to three-week period. There was some recovery in Monkeys 840, 858 and 859 but without ever attaining a normal response. Moreover, on occasions the vertically moving stripes elicited a perverted response in the horizontal plane. In the sixth animal, (No. 857), optokinetic nystagmus downward was initially present but defective (fig. 5) and returned to normal at the end of two weeks. Optokinetic after-nystagmus downward was absent in all 6 monkeys and only recovered minimally in Nos. 840 and 857, three weeks after operation.

Upward optokinetic nystagmus was absent in 3 monkeys (Nos. 842, 855, 859) and defective in a fourth animal (No. 858). It eventually recovered in all but one of these monkeys (No. 842) (fig. 5). In fact, Monkey 857 showed an enhanced optokinetic nystagmus upward as compared to its pre-operative condition, one week after operation, and in Monkey 840 such enhancement was present from the early post-operative period.

Visual stimuli moving obliquely upward, from RD→LU, and from LD→RU, which in normals elicits an optokinetic nystagmus and optokinetic after-nystagmus in an obliquely downward direction, resulted in a perverted optokinetic nystagmus in the strict horizontal plane in 4 of the animals (Nos. 842, 855, 858, 859). In the other 2 monkeys (Nos. 840 and 857), there were occasional downward components which were always much weaker than the horizontal vectors (fig. 6).

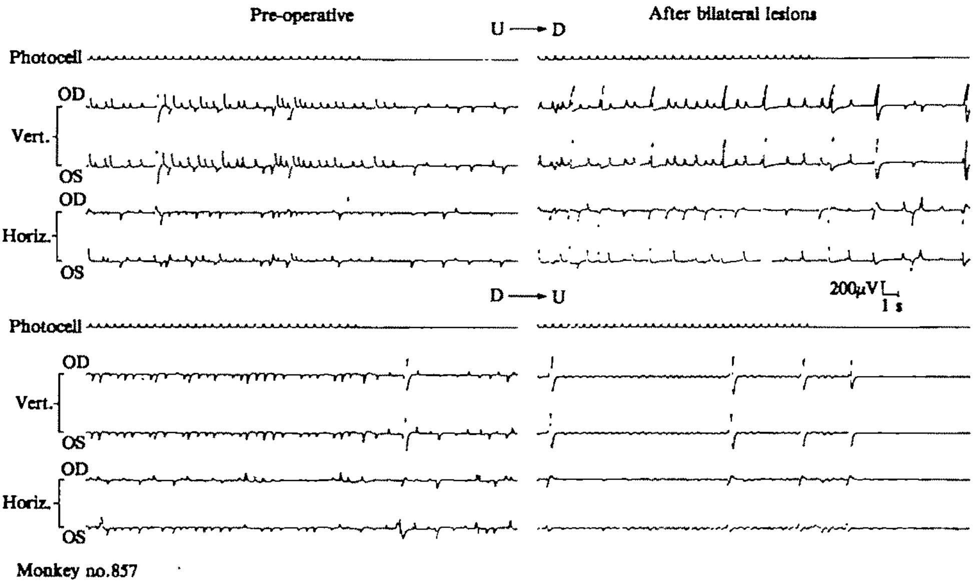


FIG. 5. Electro-oculograms during and after optokinetic stimulation in the vertical plane. Direction of moving stimuli indicated by arrows. U, up; D, down; OD, right eye; OS, left eye; Vert., vertical; Horiz., horizontal. Direction of a given rapid eye movement can be evaluated by inspection of the four channels. A straight upward movement of the eyes appears as upward deflections in the vertical channels and convergent deflections in the horizontal channels. A straight downward movement, as downward deflections in the vertical and divergent deflections in the horizontal channels. Duration and frequency of stimulation is given by the photoelectric cell tracings. When this tracing is flat (no stimulus), the response is the OKAN. Note the almost complete abolition of nystagmus downward after bilateral lesions in the prerubral fields when the stimuli moved upwards (*bottom right*). Stripes moving downward elicited an upward nystagmus with slightly reduced frequency (*top right*) as compared to the pre-operative recording (*top left*).

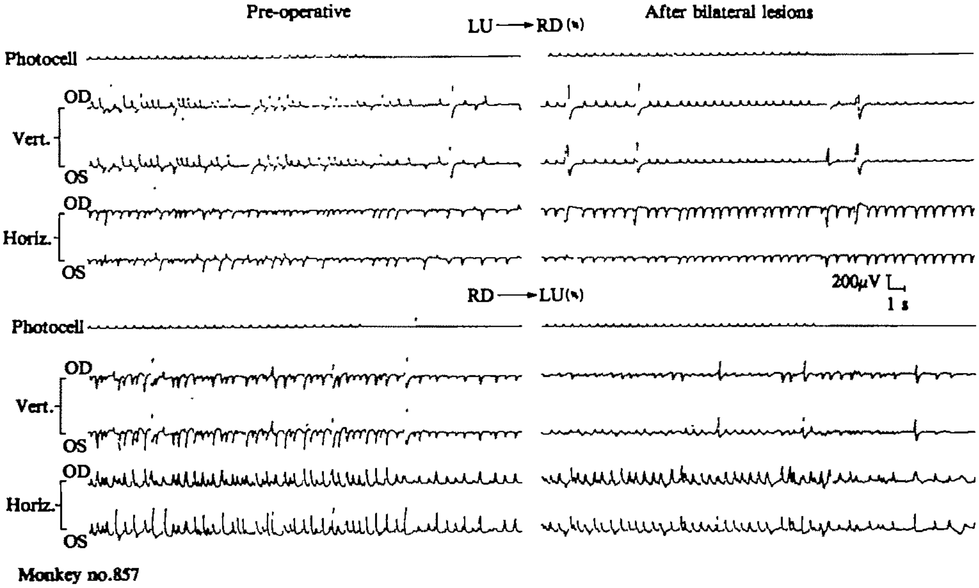


FIG. 6. Electro-oculograms during and after optokinetic stimulation in a 45 degrees oblique plane. Direction of moving stimuli indicated by arrows. LU, left and up; RD, right and down. Short arrows in parenthesis give the actual direction of movement. Notation as in fig. 5. Pre-operative recordings show normal oblique OKN and OKAN. An oblique nystagmus to the left and up, elicited by LU→RD movement of the stripes, appears as upward deflections in the vertical channels, and downward deflections in the horizontal channels. An oblique response to the right and down appears as downward deflections in the vertical channels and upward deflections in the horizontal channels. Post-operatively, the downward components are abolished so that stripes moving RD→LU result in a strictly horizontal OKN and OKAN to the right as evidenced by convergent deflections in the vertical channels and upward deflections in the horizontal channels (*bottom right*). Stripes moving from LU→RD still induce an oblique OKN upward and to the left, as indicated by upward deflections in the vertical channels and downward deflections in the horizontal channels. There are practically no upward components in the subsequent OKAN (*top right*).

The optokinetic after-nystagmus followed the same pattern as the optokinetic nystagmus elicited by obliquely upward moving stimuli, that is it was either in the horizontal direction or with very minor downward elements. Optokinetic nystagmus during stimulation from LU→RD, or RU→LD was normal, that is in the expected oblique upward direction, in 4 monkeys (Nos. 840, 857, 858, 859). In the other 2 (Nos. 842, 855), it was either in the strict horizontal plane or oblique with weaker upward vectors. The optokinetic after-nystagmus was in the same direction of the preceding optokinetic nystagmus but many times as in the normal, the vertical components were usually reversed, i.e. in the downward direction.

Optokinetic nystagmus and after-nystagmus in the horizontal plane were essentially undisturbed except for the loss of the minor vertical components in the cases showing them pre-operatively. In Monkey 842, however, responses to the right were stronger than those to the left, and sometimes optokinetic after-nystagmus to the left was absent.

Vestibular Nystagmus. Caloric tests. Pre-operatively, all monkeys showed normal oculomotor responses in both the horizontal and vertical planes, which were elicited by unilateral and bilateral irrigation respectively (fig. 7). Simultaneous irrigation of both ear canals with warm (48° C) water resulted in a high frequency (4–5 Hz) downward nystagmus sometimes associated with a slight tonic deviation of both eyes above the horizontal meridian. Bilateral stimulation with cold water (5° C) elicited a nystagmus upward with an occasional tonic deviation downward. In general, the response after the warm irrigation was of a shorter duration but of higher frequency.

Table 3 summarizes the post-operative responses to bilateral caloric tests. Warm stimulation resulted in a strong, long-lasting (up to four minutes), tonic upward deviation of the eyes in all animals. Downward nystagmus was totally abolished in 5 of these monkeys (fig. 7). In Monkey 840, there was only a weak, brief, shimmering nystagmus which never reached the horizontal meridian. The forced upward deviation subsided in Monkeys 855, 857 and 858, after fifty-three, three and nineteen days, respectively, so that thereafter there was no response to this bilateral warm caloric test. It is of interest that when this stimulus was applied to Monkey 855 on the sixth day after operation, the tonic deviation lasted for thirty-five minutes with the eyes so strongly rolled up that the cornea was barely visible below the margin of the superior eyelid. During this episode the animal was unresponsive as if it were in an ictal state from which it recovered in seven to eight hours.

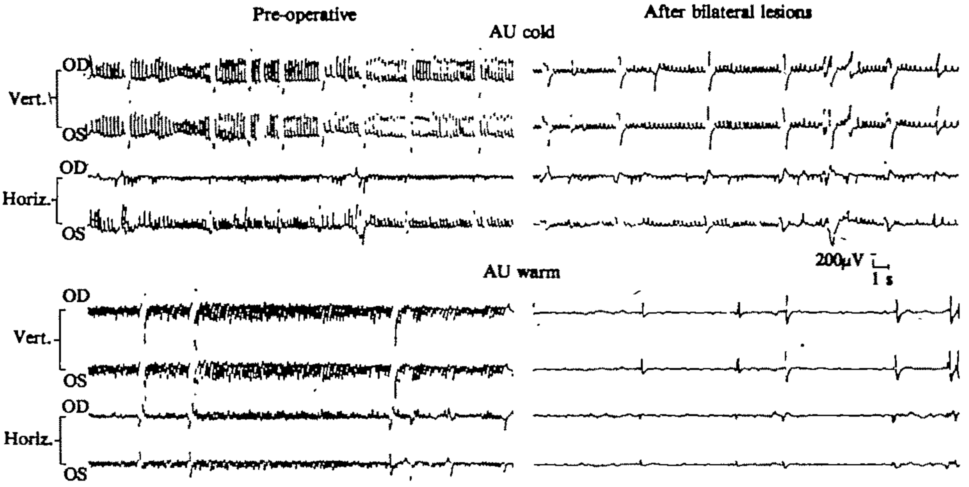


FIG. 7. Electro-oculograms of caloric nystagmus. Stimulus consisted of simultaneous irrigation of both ear canals with water at 5° C or at 48° C indicated by AU cold and AU warm respectively. Notation as in fig. 5. Direction of a given rapid eye movement can be evaluated by inspection of the four channels (*see* figs. 5 and 6). Pre-operative recordings showed normal nystagmus straight upward (*top left*) and downward (*bottom left*). Post-operatively, there is complete abolition of downward nystagmus on bilateral warm irrigation (*bottom right*). Nystagmus upward is present on bilateral cold irrigation but somewhat weaker than pre-operatively (*top right*).

TABLE 3. OCULOMOTOR RESPONSES TO BILATERAL SIMULTANEOUS CALORIC STIMULATION AFTER BILATERAL PRERUBRAL LESIONS

	Oculomotor response	
Caloric stimulus	*Slow phase*	*Quick phase*
Warm	Strong, long-lasting tonic deviation upward	Abolished or defective (shimmering) nystagmus downward above horizontal meridian
Cold	Weak to absent tonic deviation downward	Weak nystagmus upward

The results of bilateral cold irrigation were different. Three of these animals (Nos. 840, 857, 859) showed nystagmus upward which in two of them (857, 859) was of somewhat lower frequency and shorter duration than pre-operatively (fig. 7). A salient feature was that the globes moved within a space above the horizontal meridian; the quick phases upward and the tonic deviations downward both occurred above that level. In the other 3 monkeys (842, 855, 858), the vestibulo-ocular responses were initially absent. In 2, they recovered within one to three weeks, and Monkey 842 showed a persistent loss so that this monkey had no nystagmus to either cold or warm bilateral irrigations.

Unilateral cold and warm caloric tests yielded consistently normal horizontal nystagmus in all animals with bilateral lesions.

Rotational tests. Pre-operatively, clockwise rotation of the monkey while lying on the right side resulted in per-rotatory nystagmus upward and post-rotatory nystagmus downward. The direction of the response was reverse on counter-clockwise rotation. In general, the per-rotatory nystagmus was weaker than the post-rotatory response. The relative preponderance of the nystagmus downward over the nystagmus upward was similar to that observed during caloric as well as optokinetic stimulation. The results of post-operative testing paralleled those of caloric tests and are summarized in Table 4 for rotations with the animal lying on its right side. The recovery pattern was comparable to that of the caloric responses. Turning of the animals in the erect position yielded normal per- and post-rotatory nystagmus in the horizontal plane with no directional preponderance in any of the cases.

Other motor and postural disturbances. The post-operative period was stormy in 2 of the monkeys (Nos. 859 and 868) which were drowsy, occasionally lethargic and refused to eat or drink. After a forced-feeding period of two weeks, Monkey 868 recovered. The treatment continued for forty-nine days in Monkey 859 at which time the animal died. A third monkey (No. 855) had similar but milder alterations lasting one week. These monkeys had difficulties in maintaining equilibrium. Sometimes they fell to either side or backwards. There was a typical bizarre body posture. The animal stayed in a sitting position, the trunk bent

TABLE 4. OCULOMOTOR RESPONSES TO VESTIBULAR ROTATORY STIMULATION AFTER BILATERAL PRERUBRAL LESIONS

Direction of rotation (lying on the R side)	*Oculomotor response*			
	Per-rotatory		*Post-rotatory*	
	Slow phase	*Quick phase*	*Slow phase*	*Quick phase*
Clockwise	Absent deviation downward	Weak nystagmus upward	Strong long-lasting deviation upward	Abolished to strongly defective (shimmering) nystagmus downward above horizontal meridian
Counter-clockwise	Strong deviation upward	Shimmering nystagmus downward above horizontal meridian	Weak deviation downward	Weak nystagmus upward

forward with the head lying on the floor almost upside down. Occasionally, a complete somersault movement was executed. Monkey 858, after a relatively uneventful post-operative period, deteriorated rapidly and died twenty-five days after operation.

A right hemiparesis was present in Monkeys 840, 858 and 868 with absent right hopping and placing reactions. The deficit was more marked in Monkey 840 which also exhibited a right facial weakness and a right head tilt. All these disturbances improved over time and were fully recovered by two weeks except for the head tilt in Monkey 840.

Effects of Unilateral Lesions

Three of the monkeys in this study (Nos. 860, 870, 872) had the damage strictly confined to one side of the brain. As revealed in Table 1, at least one of these animals (No. 860) had a unilateral lesion in all respects comparable in location to that present in the monkeys with bilateral damage discussed above. This animal and another with a unilateral lesion (No. 872) did not show any oculomotor deficits (Table 2). Spontaneous gaze, pursuit eye movements, oculocephalic reflexes as well as the .oculomotor responses to vestibular and optokinetic stimulation were entirely normal in all planes. The third monkey (No. 870), with a right-sided lesion, exhibited a slight and transient oculomotor deficit exclusively in the contralateral horizontal plane. This animal showed a gaze preference to the right, that is, the eyes were held in the hemifield ipsilateral to the lesion, and it did not look to the left either spontaneously or on pursuit, for about one week. During this time, the vestibular nystagmus to the left could be elicited with the same frequency and duration as pre-operatively by caloric irrigation (cold water, right ear; warm water, left ear) or by sudden stop after turning the animal clockwise in the erect position. However, the quick phases of the nystagmic beats did not pass the mid-vertical meridian. The optokinetic nystagmus was difficult to evaluate because the monkey was drowsy during the examination. In short periods of alertness, however, there was no difference in the frequency between responses to the left and to the right which were also similar to pre-operative findings. In the next two weeks, the monkey was able to look spontaneously and on pursuit to the left but the eyes were still held usually in the right hemifield and were not turned as frequently to the left as to the right. In this period, the eyes crossed the vertical meridian in response to vestibular stimulation and the elicited nystagmus was entirely normal. The optokinetic responses and after responses at this time were also consistently normal.

The 3 monkeys with unilateral lesions had no deficits in vertical eye movements. Vestibular stimuli (bilateral caloric stimulation or rotation while lying on the right side), as well as vertical optokinetic stimulation yielded straight vertical upward and downward nystagmus. Convergence and pupillary reactions were normal and there was no spontaneous nystagmus. All these animals showed transient absence of hopping and placing reactions on the side opposite the lesion, but there was no manifest paresis in any of them.

DISCUSSION

The present study succeeded in delineating a circumscribed region in the monkey brain which is critically concerned with downward binocular movements. The effects of bilateral stimulation and lesion indicate that this area is centred in the classically described prerubral field on *both sides of the midline*. Indeed; *bilateral* simultaneous stimulation was most effective in eliciting downward conjugate deviation of the eyes whereas unilateral stimuli within the same region evoked this response in only one-fourth of the trials. As a rule, the downward binocular movements appeared as smooth and integrated, with a rapid rise to a maximal velocity and an immediate slowing as the position below the horizontal meridian was approached. These characteristics suggest the activation of an integrated mechanism which co-ordinates the participation of all eye muscles, either by excitation or inhibition, in the execution of the straight downward binocular deviation (Szentágothai, 1950).

To our knowledge bilateral stimulation experiments have been limited to the cerebral cortex of monkeys. True vertical eye movements were obtained from homotopic points on the surface of the frontal, occipital and pre-occipital areas (Mott and Schäfer, 1890; Crosby, Yoss and Henderson, 1952; Pasik and Pasik, 1964; Brucher, 1964). Downward deviations were consistently evoked from pre-occipital cortex above a hypothetical plane passing through the calcarine fissure. Such vertical movements were not affected by destruction of the superior colliculi (Pasik and Pasik, 1964). The present study is unique in showing a discrete downward eye movement response on bilateral simultaneous stimulation of subcortical structures. It is noteworthy that from the relatively few points where unilateral stimulation resulted in a straight or obliquely downward movement, bilateral stimuli evoked a much stronger straight downward deviation. According to the vector theory of eye movements (Bender, 1980), this result may be interpreted by mutual abolition of the horizontal vectors and summation of the vertical (downward) vectors. Bilateral stimulation of numerous foci, which on unilateral stimulation yielded only pupillary dilation and/or eye centring, induced a conjugate downward movement. Apparently, vertical eye movement vectors on either side were too weak at these locations and only bilateral activation with summation of the two vertical vectors evoked downward deviations, but weak and of shorter duration.

The reactive region for downward eye movements as determined by bilateral stimulation studies in the monkey was found to be extensive, involving elements contained within a core of tissue, about 40 mm^3 on each side. Since stimulation of various anatomical structures with just above threshold intensities evoked in most instances similar downward deviations, the responses can be attributed only to the general area and not to specific cell groups or circumscribed fibre tracts. It is significant that upward eye movements were elicited from a level about 2 mm more caudal, ventral and medial than that for downward movements. This suggests that there is a hypothetical plane separating the up and down vectors. A similar topographical pattern was found on stimulation of the occipital, pre-occipital and frontal regions of the cortex, namely, that downward movements were represented more dorsally than the upward (Mott and Schäfer, 1890; Wagman, Krieger and Bender, 1958). Likewise, stimulation of the oculomotor nerve nucleus yielded downward ocular deviations from its rostral pole, whereas upward movements were obtained from the caudal portions (Bender and Weinstein, 1942, 1943; Szentágothai, 1942).

In the past, most stimulation experiments have been limited to *one side* of the brain and this may be the reason for the rarity of obtaining true vertical eye deviations. Downward movements were only exceptionally elicited from the tegmentum of the pons and medulla, several millimetres from the midline, mainly in the area of the vestibular nuclei, as well as from the mesencephalic reticular formation and the brachium conjunctivum (Bender and Shanzer, 1964). Unilateral stimulation of the mesodiencephalic junction has resulted in a variety of ocular responses. This region was stimulated in man in the course of surgery for alleviation of involuntary movements. Most interestingly, when stimulation was applied, presumably to the fields of Forel, rostral and lateral to the red nucleus, a conjugate eye movement downward was observed in 3 of 33 patients (Spiegel, Wycis, Szekely, Soloff, Adams, Gildenberg and Zanes, 1964). In another case, however, there was oblique conjugate gaze to the contralateral side and upward (Nashold and Gills, 1967), an effect also noted in the monkey (Bender and Shanzer, 1964), together with pupillary dilation. The same region has been stimulated unilaterally in the cat with various results. In general, there were conjugate eye movements in an oblique contralateral direction upward with torsional components (Ingram, Ranson, Hannett, Zeiss and Terwilliger, 1932; Godlowski, 1938; Hess, Bürgi and Bucher, 1946; Hyde and Toczek, 1962). These effects were also noted during stimulation of the interstitial nucleus of Cajal and the nucleus of Darkschewitsch (Szentágothai, 1943; Hess *et al.*, 1946; Hyde and Toczek, 1962; Hassler, 1960). In addition, downward gaze was reported from stimulation of the so-called nucleus precommissuralis (Hassler, 1960).

In our current monkey series, unilateral stimulation resulted in no pure horizontal deviations. The horizontal components were indeed always to the opposite side, but the vertical components were stronger at all stimulated points and in all but three instances in a downward direction. The three stimulated points which yielded upward binocular movements were situated closer to the midline and more caudally. These results have been consistent over the 10 experimental animals and the difference in the type of responses as compared to the variety reported in the literature, may reflect small but significant variations in the location of the stimulating electrodes. The paucity of torsional components in the present study may have a similar explanation since the region of the nuclei of Cajal and Darkschewitsch were stimulated in few instances.

A consistent finding in all electrical stimulation experiments was a change from conjugate responses to either monocular deviations or binocular adductive movements. This transition occurred ventral and caudal to the areas yielding binocular vertical movements (*see* fig. 2). The disconjugate responses elicited within 2.5 mm from the midline could be due to direct activation of oculomotor nerve fibres on their route between the nucleus of origin and the exit at the interpeduncular fossa. The same type of reaction was obtained, however, from additional 3 mm laterally. The significance of these responses is unclear.

Eye centring movements are a well documented response to brain-stem stimulation (Bender, 1955). In the present study it was obtained from almost each point on either unilateral or bilateral stimulation and it often preceded the downward deviation. Eye centring was mostly but not necessarily associated with dilation of the pupils. The latter response was obtained from widespread areas of the thalamus and subthalamus and may be a part of a general awakening reaction. The fact that it was also evoked in fully alert patients (Nashold and Gills, 1967), however, does not support this interpretation and suggests a certain degree of specificity of the phenomenon.

It is well-known that anæsthesia depresses evoked eye movements (Livingston, 1950; Eliasson, Hyde and Bach y Rita, 1957; Bender and Shanzer, 1964). Thus it has been shown that the reactive areas for eye deviations in anæsthesized monkeys is more restricted and the oculomotor responses are less complex than in alert monkeys (Bender and Shanzer, 1964). Similarly, stimulation of brain-stem sites which yields conjugate movements before thiopental injection frequently results only in mid-positioning of the eyes after the injection (Eliasson *et al.*, 1957). Our monkeys were generally under light barbiturate narcosis. In two of the animals, however, which were more deeply anæsthesized, it was impossible to elicit conjugate eye deviation. Under this condition, only pupillary dilation and/or eye centring occurred. However, stimulation of the same points when the animal was distinctly lighter some hours later, resulted in straight downward deviations, thus confirming the dependency of the type of response on the level of anæsthesia.

The results of lesions complement those of electrical stimulation. It is quite clear that the damage to the critical prerubral region must be bilateral to cause an impairment in downward gaze, which amply supports the theory of bilateral innervation for eye movements in the vertical plane (Bender, 1960). Unilateral destruction of the same critical zone does not interrupt spontaneous and evoked vertical eye movements. A larger lesion in the fields of Forel, however, may produce a partial defect in the downward vector as revealed by bilateral vestibular stimulation (Bender and Shanzer, 1964). As for the interference with the horizontal vectors, only one of our monkeys had transient alterations in contralateral gaze after a unilateral lesion.

The deficits produced by bilateral lesions within the prerubral fields are most marked in rapid eye movements, namely spontaneous saccades and fast phases of evoked nystagmus. In fact, binocular downward saccades and downward nystagmus were the only eye movements which remained defective during the entire period of observation in all animals. Pursuit ocular movements recovered first. In most monkeys the oculocephalic reflexes were preserved even in the immediate post-operative period. On several occasions, the animals elicited their own oculocephalics by hyperextending the head to place the eyes below the horizontal meridian when stimuli were introduced in the lower visual fields. A similar posture of head directed backward together with downward position of the globes was recently observed in man (Mills and Swanson, 1978).

The findings on optokinetic testing indicated a loss of downward responses. The pattern of recovery was similar to that observed with lesions resulting in impaired horizontal or upward gaze (Bender and Shanzer, 1964; Pasik *et al.*, 1969*b*). There was initially absent optokinetic nystagmus and after-nystagmus in the direction of gaze impairment with persistent deficits particularly more marked and long lasting in the optokinetic after-nystagmus. The fact that stimulation in the oblique planes elicited strictly horizontal optokinetic nystagmus suggests that the lesions interfered with the downward vectors allowing the full emergence of the horizontal vectors contained in the oblique response. Vestibular nystagmus was also markedly affected. Not only was there a failure of the quick phases downward on bilateral warm irrigations, but the slow phases downward on cold stimulation did not go beyond the horizontal meridian.

Three of the 6 monkeys with bilateral lesions of the prerubral fields had additional alterations in upward gaze but only in the initial period. The upward gaze defect was of short duration and not so severe as that produced by bilateral lesions of the pretectum or section of the posterior commissure. Moreover, these 3 animals had no other elements of the pretectal syndrome such as pupillary alterations, eyelid retraction, lightning eye movements or spontaneous convergent nystagmus (Pasik *et al.*, 1969*a*, *b*). It should be noted that 4 out of the 10 monkeys with pretectal lesions reported previously had disturbances in downward gaze in addition to the paralysis of upward gaze. Only one of these animals had an extension of the damage into the subthalamic region on one side. It appears that when the lesion is closer to the oculomotor nerve nucleus there is interference with both upward and downward gaze suggesting a convergence of the pathways from the pretectum and the prerubral fields.

For the clinician, the question of the precise anatomical locus critical for downward gaze can be answered in part by the present results. In the monkey, a highly selective impairment of downward gaze can be caused by a lesion confined bilaterally to a small area, about 1.7 mm in diameter, rostral and dorsal to the oral pole of the red nucleus. Only the very rostral portion of the latter structure is involved and the fasciculus retroflexus is conspicuously spared. This area, the damage of which seems therefore to be sufficient to produce a downward gaze palsy, is included in all of the more extended lesions (fig. 4). It should be emphasized that this region is rather small compared with the widespread location whence bilateral stimulation results in a downward deviation. We have no information as to the degree and pattern of ocular defects which would result from lesions involving the entire excitable area.

The question of whether the oculomotor deficit in the downward direction is due to destruction of cells or of fibres arising from other locations and traversing the area, cannot be answered by lesion studies alone. It is significant, however, that extracellular recordings obtained from the same general location showed a predominance of units with bursts of activity preceding rapid eye movements in planes only 10 to 20 degrees away from the vertical (Büttner, Büttner-Ennever and Henn, 1977). These findings suggested the presence of neurons coding the direction of movement and change in position of the eyes along an almost vertical plane. It is reasonable to speculate that bilateral activation of this neuronal system could result in strictly vertical movements. In the latter study, there were units firing maximally with oblique downward movements and others with oblique upward deviations. Moreover, the tilt from the vertical occurred either to the contralateral or to the ipsilateral side. It is possible that those neurons discharging in relation to upward and/or ipsilateral vectors represent a population with inhibitory properties influencing antagonistic effectors during downward, and oblique downward and contralateral movements.

The cell groups which are present in the mesodiencephalic junction have been one of the most confusing subjects in neuroanatomy as emphasized in a recent comprehensive review (Büttner-Ennever and Büttner, 1978). It is clear, however, that the locus of lesion in the present study essentially spares the interstitial nucleus of Cajal, the nucleus of Darkschewitsch and the interstitial nuclei of the posterior commissure. The critical zone is restricted to areas rostral to these latter structures, and it appears centred in the prerubral fields on each side of the midline. A discrete cellular mass was delineated in this area of the monkey brain (Kreig, 1948), and recently named as the rostral interstitial nucleus of the medial longitudinal fasciculus (iMLF) to differentiate it from the classic interstitial nucleus of Cajal (Büttner-Ennever and Büttner, 1978). The latter investigators succeeded in tracing a discrete projection from the paramedian zone of the pontine reticular formation to the rostral iMLF, and from it to the oculomotor nerve nucleus, all on the same side. This anatomical connectivity not only links the PPRF, which is an essential region for eye movement control (Cohen, 1974), with a cell group possibly involved in downward gaze mechanisms, but also helps to understand why bilateral PPRF lesions interfere with both horizontal and vertical eye movements (Bender and Shanzer, 1964). More recently, a projection to the oculomotor nucleus from a somewhat wider area apparently including the rostral iMLF and the nucleus campi Foreli has also been described in the cat and monkey (Graybiel, 1978). The rostral iMLF may be identical to a nucleus named prestitialis in the cat (Hassler, 1960; Büttner-Ennever and Büttner, 1978). It has been reported, however, that unilateral stimulation of the latter structure elicits raising movements of the eyes and head, and its destruction leads to a lowering posture of the head (Hassler, 1960). It is indeed difficult to reconcile the latter findings with those of the present study which require *bilateral* stimulation or lesion to influence predominantly downward and not upward movement of the eyes. It was recently reported that bilateral lesions in the 'reticular nucleus of the mesencephalic tegmentum' (Denny-Brown and Fischer, 1976), later called 'area tegmentalis' (Denny-Brown, 1977), resulted in upward and downward gaze paralysis with some limitation of lateral gaze as well. Upon recovery, some of these monkeys remained only with upward gaze defects while at least one 'showed most commonly an absence of downward movement' (Denny-Brown, 1977, p. 65). Apparently, the bilateral destruction differed in its location over the group, in some cases including and in others being caudal to those of the present study. No correlation can be made, however, between the precise level of the damage and gaze defects in the upward or downward direction. Finally, it is doubtful that the critical lesion included to any extent the 'formation grise cupuliforme periretrorubrique' of Foix and Nicolesco (1925) which was implicated in downward gaze mechanisms by Muskens (1933) on the basis of Schuster's case (1921).

There are five clinicopathological cases of paralysis of downward gaze (Schuster, 1921—Muskens, 1934; André-Thomas, *et al.*, 1933; Jacobs, *et al.*, 1973; Cogan, 1974; Halmagyi *et al.*, 1978), which as mentioned in the introduction served to plan the present experiments. As depicted in Table 5, the common denominator was an absence of downward saccades. The downward movements on pursuit of targets or during the oculocephalic manœuvre were present in the first two patients, abolished in the third, and not reported in the last two. Convergence was possible in the second case and not reported in the first and fifth. Pupils were normal only in the fifth case.

TABLE 5. OCULAR SIGNS AND PATHOLOGICAL FINDINGS IN PATIENTS WITH ISOLATED DOWNWARD GAZE PALSY

	Downward eye movements											
Cases	*Saccades*	*Pursuit*	*Oculocephalics*	*Convergence*	*Pupillary reflexes*	*Prerubral field*	*Red nucleus*	*Fasciculus retroflexus*	*Thalamus*	*III nerve nucleus*	*N of Cajal*	*N. of Darkschewitsch*
1. Schuster, 1921; Muskens, 1934	0	+	+++	?	Sluggish	X		x	X		R	
2. André-Thomas *et al.*, 1933	0	+	++	+	Sluggish	X	x	?	r			X
3. Jacobs *et al*, 1973	0	0	0	0	Sluggish	X		X	X	x	x	x
4. Cogan, 1974*	0	?	?	0	Sluggish	X	R	?	X	?	?	?
5. Halmagyi, *et al.*, 1978†	0	?	?	?	Normal	L	Lr	X	L		L	L

0 = absent; +, ++, +++ = minimally present to normal; ? = not reported. X, x, R, r, L, as in Table 1.

* This case was reported to show also 'internuclear ophthalmoplegia' so that in the strict sense it was not an isolated paralysis of downward gaze. † Since the red nucleus and fasciculus retroflexus are also involved on the right side, it is possible that alterations of the critical zone are in fact bilateral and not strictly confined to the left side.

The analysis of the histological findings reveals that the critical area delineated in the present study was destroyed bilaterally in all five patients. The additional involvement of the fasciculus retroflexus has led some investigators to speculate on its importance for downward gaze mechanisms (Jacobs *et al.*, 1973; Halmagyi, *et al.*, 1978). The findings in the monkeys, however, exclude this possibility since the critical lesion is located rostral to the fasciculus retroflexus and completely spares this structure (fig. 4). Most of the patients showed also extensive lesions of thalamic nuclei as a result of vascular disease affecting the so-called posterior thalamo-subthalamic paramedian artery (Percheron, 1966). Branches of the equivalent vessel in the monkey brain are present at the medial limit of the rostral iMLF as already noted by others (Büttner-Ennever and Büttner, 1978). It is not surprising, therefore, that in three of our monkeys where the electrolysis destroyed these arterioles, additional bilateral infarcts were present in the thalamus. Whether this damage was responsible for the initial lethargy, also exhibited by most of the patients discussed above, is not clear since only two of the three monkeys had this condition. It is interesting that the two animals that died four to seven weeks after operation exhibited total bilateral retrograde degeneration of the substantia nigra, pars compacta as a result of interruption of the nigrostriatal pathway.

SUMMARY

Ten monkeys were stimulated unilaterally and bilaterally through bipolar electrodes placed stereotactically on each side of the midline under light barbiturate anæsthesia. Bilateral simultaneous stimulation elicited straight downward binocular movements from a core of tissue about 40 mm^3 on each side which included the fields of Forel, zona incerta, subthalamic nucleus, oral pole of the red nucleus, fasciculus retroflexus and 'area tegmentalis'. Unilateral stimulation of the same points yielded downward eye movements in only 25 per cent of the instances. Upward deviation of the globes could be elicited by bilateral stimulation of tissue located more caudal, ventral and medial than that from which downward movements were obtained.

Bilateral electrolytic lesions within the region outlined above caused significant defects in downward gaze both in saccadic and slow pursuit binocular movements. Passive bending of the head backwards, however, resulted in downward deviation of the globes (oculocephalic reflex). Optokinetic nystagmus and after-nystagmus downward were abolished. Oblique (45 degrees) optokinetic stimulation elicited a perverted response in the horizontal plane. Vestibulo-ocular reflexes elicited by bilateral warm irrigation of both ear canals with the monkey in the erect position, or by turning the animal while lying on one side, caused a strong tonic deviation upward with absence of nystagmus downward. Some of these monkeys showed additional alterations in upward gaze but they were less severe in intensity and duration than those of downward gaze. All eye deviations in the horizontal plane were consistently normal. Recovery occurred in all types of vertical binocular

movements except in the rapid motions (saccades and quick phases of nystagmus) below the horizontal meridian. A unilateral lesion had no effect.

The minimal damage producing downward gaze defects was about 1.7 mm in diameter, centred in the prerubral fields, rostral and medial to the red nuclei with minimal involvement of the oral pole of these structures. The nuclei of Cajal, Darkschewitsch and interstitialis of the posterior commissure, as well as the fasciculus retroflexus and the posterior commissure, were spared by this lesion. The so-called rostral interstitial nucleus of the medial longitudinal fasciculus and the nucleus campi Foreli appear to be destroyed. These structures are known to receive an input from the paramedian pontine reticular formation and project on to the oculomotor nerve nucleus.

These results demonstrate that the prerubral fields contain structures which are critical for rapid eye movements downward, and therefore an isolated downward gaze palsy is a strong indicator of a bilateral lesion of this zone. The findings in the few reported cases with this sign and available pathological analysis suggest that our conclusions from the experimental monkey apply to man as well. The concept of bilateral innervation for vertical eye movements is amply confirmed for the downward vectors. There appears to be a hypothetical plane separating the downward from the upward vectors similar to that found in the cerebral cortex where downward movements are represented more dorsally than the upward deviations.

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REFERENCES

André-Thomas, Schaeffer, H. and Bertrand, I. (1933) Paralysie de l'abaissement du regard, paralysie des inférogyres, hypertonie des supérogyres et des releveurs des paupières. *Révue Neurologique*, **40**, 535–542.

Baker, R. and Highstein, S. M. (1975) Physiologic identification of interneurons and motoneurons in the abducens nucleus. *Brain Research, Amsterdam*, **91**, 292–298.

Bender, M. B. (1955) The eye centering system. *AMA Archives of Neurology and Psychiatry*, **73**, 685–699.

—— (1960) Comments on the physiology and pathology of eye movements in the vertical plane. *Journal of Nervous and Mental Disease*, **130**, 456–466.

BENDER, M. B. (1980) Organization of oculomotor pathways. *Brain*. In press.

—— and SHANZER, S. (1964) Oculomotor pathways defined by electrical stimultion and lesions in the brainstem of monkey. In: *The Oculomotor System*. Edited by M. B. Bender. New York: Harper and Row, pp. 81–140.

—— and WEINSTEIN, E. A. (1942) The functional pattern within the oculomotor nucleus. *Transactions of the American Neurological Association*, **68**, 48–51.

—— —— (1943) Functional representation in the oculomotor and trochlear nuclei. *Archives of Neurology and Psychiatry*, **49**, 98–106.

BRUCHER, J. M. (1964) *L'Aire Oculogyre Frontale du Singe. Ses Fonctions et ses Voies Efférentes.* Bruxelles: Arscia, p. 69.

BÜTTNER, U., BÜTTNER-ENNEVER, J. A. and HENN, V. (1977) Vertical eye movement related unit activity in the rostral mesencephalic reticular formation of the alert monkey. *Brain Research, Amsterdam*, **130**, 239–252.

BÜTTNER-ENNEVER, J. A. and BÜTTNER, U. (1978) A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. *Brain Research, Amsterdam*, **151**, 31–47.

—— and HENN, V. (1976) An autoradiographic study of the pathways from the pontine reticular formation involved in horizontal eye movements. *Brain Research, Amsterdam*, **108**, 155–164.

CARPENTER, M. B., MCMASTERS, R. E. and HANNA, G. R. (1963) Disturbances of conjugate horizontal eye movements in the monkey. *Archives of Neurology, Chicago*, **8**, 231–247.

CHRISTOFF, N. (1974) A clinicopathologic study of vertical eye movements. *Archives of Neurology, Chicago*, **31**, 1–8.

COGAN, D. C. (1974) Paralysis of down-gaze. *Archives of Ophthalmology*, **91**, 192–199.

COHEN, B. (1974) The vestibulo-ocular reflex arc. In: *Handbook of Sensory Physiology*. Volume 6 Part 1. Edited by H. H. Kornhuber. Berlin-Heidelberg-New York: Springer, pp. 477–549.

CROSBY, E. C., YOSS, R. E. and HENDERSON, J. W. (1952) The mammalian midbrain and isthmus regions. Part II. The fiber connections. D. The pattern for eye movements on the frontal eye field and the discharge of specific portions of this field to and through midbrain levels. *Journal of Comparative Neurology*, **97**, 357–383.

DENNY-BROWN, D. (1977) Spasm of visual fixation. In: *Physiological Aspects of Clinical Neurology*. Edited by F. C. Rose. Oxford: Blackwell, pp. 43–75.

—— and FISCHER, E. G. (1976) Physiological aspects of visual perception. II. The subcortical visual direction of behavior. *Archives of Neurology, Chicago*, **33**, 228–242.

ELIASSON, S. G., HYDE, J. E. and BACH-Y-RITA, P. (1957) Effect of intravenous thiopental on spontaneous and evoked eye movements in cats. *American Journal of Physiology*, **191**, 203–208.

FOIX, C. and NICOLESCO, J. (1925) *Les Noyaux Gris Centraux et la Région Mésencéphalosous-optique.* Paris: Masson, pp. 440–444.

GODLOWSKI, W. Experimentelle Untersuchungen über die durch Reizung des Zwischen- und Mittelhirns hervorgerufenen assoziierten Augenbewegungen. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **162**, 160–182.

GRAYBIEL, A. M. (1978) Organization of oculomotor pathways in the cat and rhesus monkey. In: *Control of Gaze by Brainstem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier, pp. 79–88.

—— and HARTWEIG, E. A. (1974) Some afferent connections of the oculomotor complex in the cat: an experimental study with tracer techniques. *Brain Research, Amsterdam*, **81**, 543–551.

HALMAGYI, G. M., EVANS, W. A. and HALLINAN, J. M. (1978) Failure of downward gaze. *Archives of Neurology, Chicago*, **35**, 22–26.

HASSLER, R. (1960) Thalamo-corticale Systeme der Körperhaltung und der Augenbewegungen. In: *Structure and Function of the Cerebral Cortex*. Edited by D. B. Tower and J. P. Schadé. Amsterdam: Elsevier, pp. 124–130.

HESS, W. R., BÜRGI, S., and BUCHER, V. (1946) Motorische Funktionen des Tektal-und Tegmentalgebietes. *Monatsschrift für Psychiatrie und Neurologie*, **112**, 1–52.

HYDE, J. E. and TOCZEK, S. (1962) Functional relation of interstitial nucleus to rotatory movements evoked from zona incerta stimulation. *Journal of Neurophysiology*, **25**, 455–466.

INGRAM, W. R., RANSON, S. W., HANNETT, F. I., ZEISS, F. R. and TERWILLIGER, E. H. (1932) Results of stimulation of the tegmentum with the Horsley-Clarke stereotaxic apparatus. *Archives of Neurology and Psychiatry*, **28**, 513–541.

JACOBS, L., ANDERSON, P. J. and BENDER, M. B. (1973) The lesions producing paralysis of downward but not upward gaze. *Archives of Neurology, Chicago*, **28**, 319–323.

KÖMPF, D., PASIK, T. and PASIK, P. (1977) Critical structures for downward gaze in monkeys. *Neuroscience Abstracts*, **3**, 156.

KRIEG, W. J. S. (1948) A reconstruction of the diencephalic nuclei of Macacus rhesus. *Journal of Comparative Neurology*, **88**, 1–51.

LIVINGSTON, R. B. (1950) Ipsilaterale und kontralaterale Augenbewegungen des frontalen okulomotorischen Gebietes des Affen. *Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **185**, 690–700.

MILLS, R. P. and SWANSON, P. D. (1978) Vertical oculomotor apraxia and memory loss. *Annals of Neurology*, **4**, 149–153.

MOTT, F. W. and SCHÄFER, E. A. (1890) On associated eye movements produced by cortical faradization of the monkey's brain. *Brain*, **13**, 165–173.

MUSKENS, L. J. J. (1933) La base anatomique des positions forcées des yeux soi-disant paralysies du regard. *Révue Neurologique*, **40 (2)**, 287–296.

—— (1934) *Das Supra-Vestibulare System bei den Tieren und beim Menschen, mit besonderer Berucksichtigung der Klinik der Blicklähmungen, der sogen. Stirnhirnataxie, der Zwangsstellungen und der Zwangsbewegungen*. Amsterdam: Noord-Hollandsche Uitgeversmaatschappij, pp. 244–255.

NASHOLD, B. S., Jr. and GILLS, J. P. (1967) Ocular signs from brain stimulation and lesions. *Archives of Ophthalmology*, **77**, 609–618.

OLSZEWSKI, J. (1952) *The Thalamus of the Macaca Mulatta. An Atlas for Use with the Stereotaxic Instrument*. Basel-New York: Karger, pp. 13–17.

PAPEZ, J. W. (1942) A summary of fibre connections of the basal ganglia with each other and with other portions of the brain. *Research Publications of the Association for Research in Nervous and Mental Disease*, **21**, 21–68.

PASIK, P. and PASIK, T. (1964) Oculomotor function in monkeys with lesions of the cerebrum and the superior colliculi. In: *The Oculomotor System.* Edited by M. B. Bender, New York: Harper and Row, pp. 40–80.

—— —— and BENDER, M. B. (1969*a*) The pretectal syndrome in monkeys: I. Disturbances of gaze and body posture. *Brain,* **92,** 521–534.

—— —— VALCIUKAS, J. A. and BENDER, M. B. (1971) Vertical optokinetic nystagmus in the split-brain monkey. *Experimental Neurology,* **30,** 162–171.

—— VALCIUKAS, J. A. and PASIK, T. (1973) Effect of head and body tilt on flicker-induced nystagmus in monkeys. *Experimental Neurology,* **41,** 15–28.

PASIK, T. and PASIK, P. (1975) Experimental models of oculomotor dysfunction in the rhesus monkey. In: *Advances in Neurology,* Vol. 10. *Primate Models of Neurological Disorders.* Edited by B. S. Meldrum and C. D. Marsden. New York: Raven Press, pp. 77–89.

—— —— and BENDER, M. B. (1966) The superior colliculi and eye movements. An experimental study in the monkey. *Archives of Neurology, Chicago,* **15,** 420–436.

—— —— —— (1969*b*) The pretectal syndrome in monkeys. II. Spontaneous and induced nystagmus and 'lightning' eye movements. *Brain,* **92,** 871–884.

PERCHERON, G. (1966) *Etude Anatomique du Thalamus de l'Homme Adulte et de sa Vascularisation Artérielle.* Paris: Thèse, pp. 1–350.

SCHÄFER, E. A. (1900) The cerebral cortex. In: *Textbook of Physiology,* Vol. 2. Edited by E. A. Schäfer. Edinburgh and London: Petland, pp. 697–782.

SCHUSTER, P. (1921) Zur Pathologie der vertikalen Blicklahmung. *Deutsche Zeitschrift fur Nervenheilkunde,* **70,** 97–115.

SHANZER, S. and BENDER, M. B. (1959) Oculomotor responses on vestibular stimulation of monkeys with lesions of the brain-stem. *Brain,* **82,** 669–682.

SPIEGEL, E. A., WYCIS, H. T., SZEKELY, E. G., SOLOFF, L., ADAMS, J., GILDENBERG, P. and ZANES, C. (1964) Stimulation of Forel's field during stereotaxic operations in the human brain. *Electroencephalography and Clinical Neurophysiology,* **16,** 537–548.

SZENTÁGOTHAI, J. (1942) Die innere Gliederung des Oculomotoriuskernes. *Archiv für Psychiatrie und Nervenkrankheiten,* **115,** 127–135.

—— (1943) Die zentrale Innervation der Augenbewegungen. *Archiv für Psychiatrie und Nervenkrankheiten,* **116,** 721–760.

—— (1950) Recherches expérimentales sur les voies oculogyres. *Semaine des Hôpitaux de Paris,* **26,** 2989–2995.

WAGMAN, I. H., KRIEGER, H. P. and BENDER, M. B. (1958) Eye movements elicited by surface and depth stimulation of the occipital lobe of Macaque mulatta. *Journal of Comparative Neurology,* **109,** 169–193.

WHITTERIDGE, D. (1960) Central control of eye movements. In: *Handbook of Physiology.* Sect. I, Vol. 2. Edited by J. Field, H. W. Magnum and V. E. Hall. Washington: American Physiological Society, pp. 1089–1110.

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Brain (1979), **102**, 559–580

LEBER'S OPTIC NEUROPATHY

A CLINICAL AND VISUAL EVOKED POTENTIAL STUDY OF AFFECTED AND ASYMPTOMATIC MEMBERS OF A SIX GENERATION FAMILY

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INTRODUCTION

LEBER'S disease is a familial form of optic neuropathy which predominantly affects young males, leading to acute or subacute sequential binocular failure of central vision and optic atrophy. In spite of extensive family studies (Leber, 1871; Lundsgaard, 1944; Van Senus, 1963; Seedorf, 1968*a*, *b*, 1969*a*, *b*; Waardenberg, 1969; Seedorf, 1970; Wallace, 1970) the mode of transmission of the disease has not been satisfactorily determined. Indeed the pattern of inheritance appears to be unique and cannot be adequately accounted for on the basis of X-linked recessive transmission as females are affected and transmit the carrier state to their daughters more frequently than would be expected (Imai and Moriwaki, 1936; Rønne, 1944; Colenbrander, 1962; Seedorf, 1969*b*, 1970; Went, 1972). Nevertheless, it is known that the disorder is transmitted exclusively in the female lineage, no male who has not himself married a carrier having transmitted the disease, and the daughters of affected males being neither affected nor carriers. As the inheritance pattern cannot be explained by conventional Mendelian principles, the possibility of transmission by non-chromosomal means, perhaps involving the transfer of a slow virus-like agent (Wallace, 1970; Erikson, 1972) in the maternal ooplasm (Imai and Moriwaki, 1936; Rønne, 1944; Colenbrander, 1962) or transplacentally (Erikson, 1972; Harper, 1977) has been suggested.

Despite suggestions of an underlying defect of cyanide metabolism (Wilson, 1965), the evidence implicating a toxic or metabolic disturbance has been inconclusive. The factors determining the time of onset of visual loss and the temporal relationship between involvement of the two eyes are also unknown, as is the significance of associated neurological deficits in some families (Wilson, 1963; Lees,

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MacDonald and Turner, 1964; Went, 1972; Wallace, 1970; McLeod, Low and Morgan, 1978).

As the condition is not lethal there has been little opportunity to study the pathological changes in the visual pathway. The literature contains only a few reports of cases studied at post-mortem, all of whom had long-standing optic neuropathy. These studies showed extensive axonal degeneration and loss of myelin in the central portions of the optic nerves (Rehsteiner, 1930; Kwittken and Barest, 1958; Wilson, 1963; Adams, Blackwood and Wilson, 1966; Oud, Henneman, Brugge, Hariga and Martin, 1968). As no case in the early stages of the disease has been studied histologically, the nature of the initial lesion in the optic nerve remains uncertain.

The present study was undertaken to document more fully the clinical and visual evoked potential (VEP) findings in affected members of a family with typical Leber's optic neuropathy, and to determine whether there are characteristic abnormalities of the VEP which might give further insight into the nature of the pathological process. In addition, 40 asymptomatic members derived from male and female lineages were studied with the following questions in mind. First, is the disease expressed in subclinical form prior to the onset of visual impairment, and if so is it possible to detect those individuals in the female lineage who will go on to develop visual failure? Secondly, is the disease expressed in subclinical form in clinically unaffected female carriers with one or more affected male offspring, or in potential carriers? Thirdly, is there any evidence of transmission of a subclinical form of the disease by affected or unaffected males?

MATERIALS AND METHODS

The family was derived from the union of a Chinese male and an Irish female and comprised 91 members in 6 generations (fig. 1). Of the 30 affected individuals 23 were males, representing 60.5 per cent of males descended from female lineages and at risk of developing the disease. Of these, 4 were the offspring of affected females and 19 of unaffected females. Some of the affected cases were included in earlier reports of this family (Morlet, 1921; Rogers, 1977). Further analysis of the pedigree showed that there were 20 obligate female carriers who were either themselves clinically

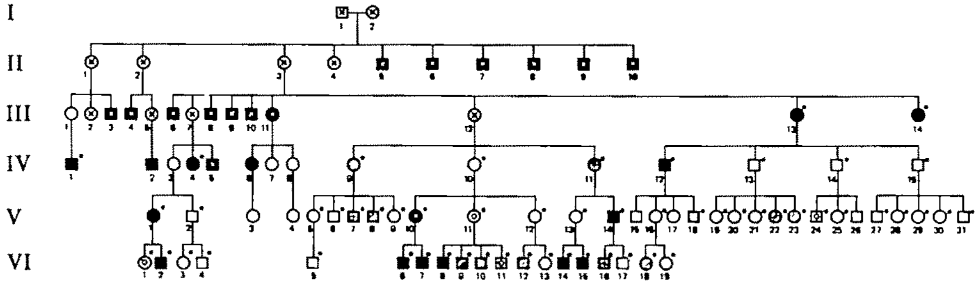


FIG. 1. Six generation pedigree of the family with Leber's optic neuropathy showing details of affected and asymptomatic members studied and of the abnormalities found. □ = male. ○ = female. ● ■ = affected. x = deceased. • = clinical and VEP examination. ⊚ ⊠ = asymptomatic; normal VEP; mild clinical abnormalities. ○ □ = asymptomatic; atypical or mildly abnormal VEP.

affected or whose offspring had the disease. On the other hand, no affected male was known to have transmitted the disease to his offspring. At the time of the study there were 67 living members, 54 of whom were available for examination, 14 of these being clinically affected and the remaining 40 being asymptomatic. The 14 affected individuals had all suffered acute or subacute monocular loss of central vision which in all but 2 cases was followed by involvement of the second eye within one year. The mean age of the group was 38 years (13–81 years) and the mean age of onset of visual loss was 23 years (5–49 years). Of the 40 asymptomatic members studied, 21 were descendants from the female lineage and were at risk of developing or transmitting the disease, while the remaining 19 were derived from male lineages.

The neuro-ophthalmic examination included measurements of visual acuity (Snellen and Jaeger charts), testing of colour vision (Ishihara plates), mapping of central and peripheral visual fields, ophthalmoscopy, and assessment of pupil size, pupillary reactions and ocular movements. The degree of pallor of the optic discs and of tortuosity of the peripheral retinal vessels were each graded on a scale of 0 (normal) to 4 (marked optic atrophy or vessel tortuosity). In addition, counts of the numbers of small vessels crossing the perimeter of the optic disc (excluding those recognizable as veins or arteries) were made in each eye (Veith and Sacks, 1973). For comparative purposes similar observations were made in 75 normal subjects 5–61 years of age. Of these only 3 (4 per cent) made a single error with the Ishihara plates and none took longer than five seconds to identify each plate. All had 7 or more small vessels crossing the disc margin with the exception of 2 who had 6 (range 6–13; mean 8.7). Fundus photographs were used for vessel counts and for assessment of vessel tortuosity in some subjects. Affected and asymptomatic members were subjected to the same examination during one of 3 one-day sessions. The examiner was unaware at the time of whether or not asymptomatic subjects were in the 'at risk' group. A full neurological examination was also performed in each of the 54 family members studied.

Pattern-reversal VEPs were recorded using a technique which has been described in detail elsewhere (Collins, Black and Mastaglia, 1978). Responses were recorded from an active electrode at 0z (10–20 system) during central field (3 degrees radius; 12′ checks) monocular stimulation. Appropriate spectacles were worn by subjects with refractive errors. Responses were displayed on a Tektronix 4010 terminal. In addition to measurement of the latency of the major positive component (P2 or $\overline{\text{P100}}$) of the response, a number of other parameters of latency, relative delay, temporal dispersion and amplitude were also measured for each response, normal ranges for these parameters having previously been established in a control group of 50 subjects 17–65 years of age (Collins *et al.*, 1978). Included in these parameters was the interval between the negative peaks preceding and following the P2 or $\overline{\text{P100}}$ peak, which was taken as a measure of the degree of temporal dispersion of the response. A detailed comparison of the responses obtained from stimulation of the two eyes was also made, using a cross-correlation programme. For logistic reasons 4 affected subjects and 4 asymptomatic subjects who live in New South Wales were studied in another laboratory (Drs K. Lethlean and N. Skuse) using a similar technique, which employed monocular pattern-reversal stimulation and mid-line occipital recording, but one in which the radius of the retinal field stimulated was wider (15 degrees instead of 3 degrees) and the visual subtense of the check size larger (50′ instead of 12′). The only response parameter measured in these subjects was the latency of the P2 component, which was related to the established normal range in that laboratory.

RESULTS

Affected Subjects

Neuro-ophthalmic findings. The frequency of various neuro-ophthalmic findings is shown in fig. 2. Defective colour vision, optic disc pallor, central scotomata and reduced visual acuity were the most frequent findings in that order. Seven subjects were certifiably blind, 2 had visual acuities of 6/24 and 6/36 in one eye and normal

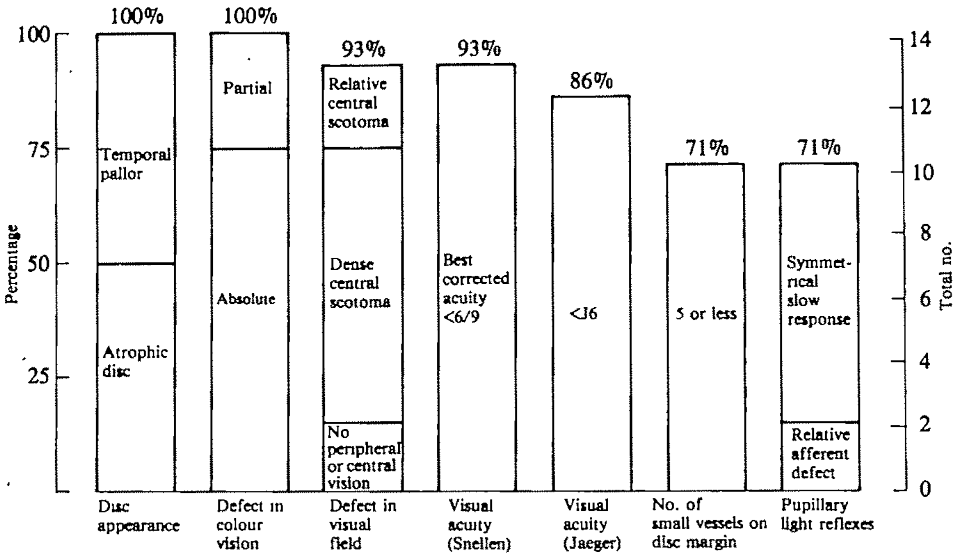


FIG. 2. Relative frequency of neuro-ophthalmic findings in clinically affected subjects.

acuity in the other eye, while the visual acuities in the remainder ranged from 6/60 to 6/5. Three subjects, including the 2 with monocular involvement, had normal colour vision in one eye. With the exception of Case V.14, all the other affected cases had unilateral or bilateral relative or absolute central scotomata of varying sizes. Pupillary light responses were normal in 4 subjects, bilaterally sluggish in 8, and 2 showed a relative afferent pupillary defect. Seven subjects had marked bilateral

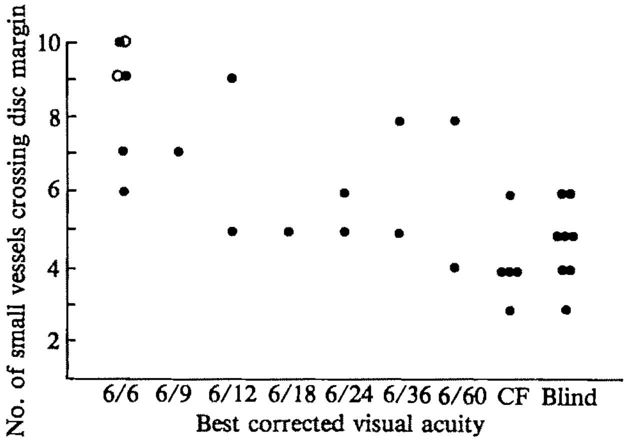


FIG. 3. Relationship between visual acuity (Snellen) and the number of small vessels crossing the disc margin in clinically affected subjects (*see text*). The open circles represent the asymptomatic eye in the two patients with purely monocular involvement.

optic atrophy, while 7 had only temporal pallor of the optic disc which was bilateral in 4 and unilateral in 3.

The number of small vessels crossing the disc margin was reduced to 6 or less in both eyes in 9 subjects, and in one eye in two. As shown in fig. 3 there was a correlation between reduced visual acuity and reduced small vessel numbers (Spearman ranking correlation coefficient (r_s) = 0.64, $P < 0.01$). There was also a correlation between the vessel count and the appearance of the optic disc. All but one of the 14 eyes showing advanced optic atrophy had 6 or fewer small vessels crossing the disc margin (mean 4.8), while in those eyes showing only temporal pallor the vessel count ranged from 4 to 9 (mean 6.5) (fig. 4). As shown in fig. 5 there was also a correlation between the visual acuity and the degree of optic atrophy. There was no correlation between the severity of any of these clinical parameters and the duration of the disease.

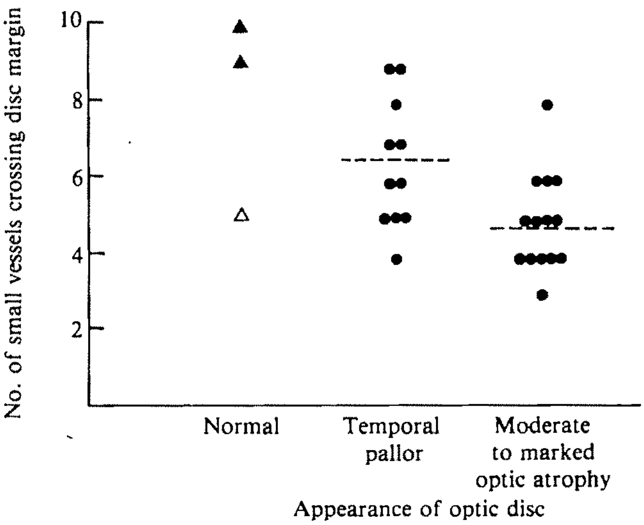


FIG. 4. Relationship between the number of small vessels crossing the disc margin and the ophthalmoscopic appearance of the optic disc in clinically affected subjects. △ = normal disc with papillomacular fibre bundle atrophy. ▲ = asymptomatic eye.

Tortuosity of the peripheral retinal vessels was a striking feature in one subject (VI.8) who had monocular visual involvement but bilateral tortuosity, and it was also prominent in 5 other cases (fig. 6). Five subjects with advanced optic atrophy exhibited the characteristic attenuation of the retinal vasculature. Two elderly females (III.13 and III.14) who had sustained the typical sequential bilateral loss of central vision leading to blindness in their mid-twenties showed additional ophthalmoscopic abnormalities. In Case III.13 there was bilateral disciform retinal degeneration, while Case III.14 had extensive retinal drusen.

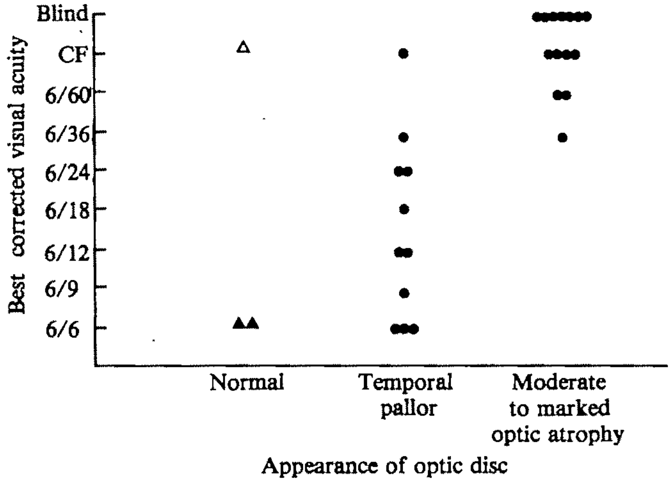
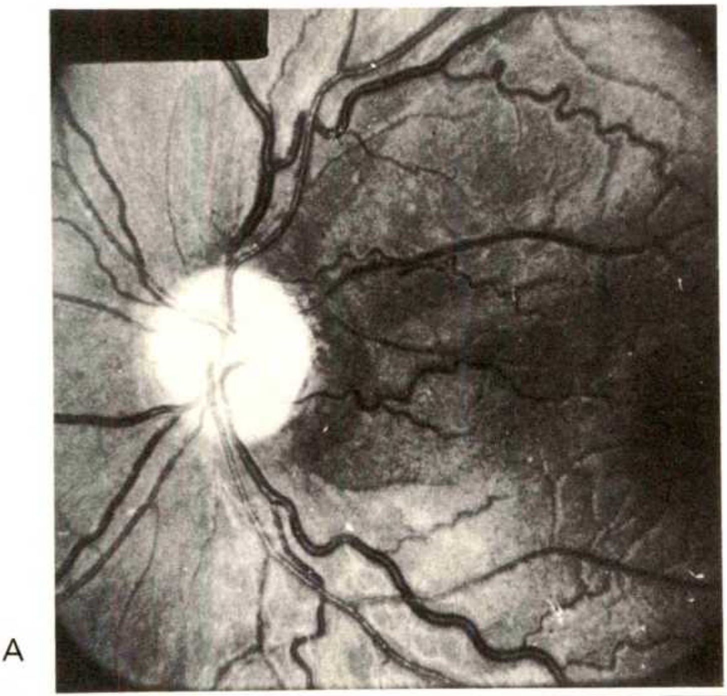


FIG. 5. Relationship between the visual acuity (Snellen) and the ophthalmoscopic appearance of the optic disc in clinically affected subjects. △ = normal disc with papillomacular fibre bundle atrophy. ▲ = asymptomatic eye.

Visual evoked potential findings. The VEP findings in the 14 clinically affected members are summarized in Table 1. In 9 there was no recognizable response from either eye. The findings in the remaining 5 cases were variable. In one case (VI.14) with bilateral involvement clinically, both VEPs were delayed, widened and reduced in amplitude (fig. 7A). In 2 subjects with monocular involvement the response on the affected side was grossly abnormal while that from the other eye was normal in one (V.10) (fig. 7B), and widened with a normal latency in the other (VI.8) (fig. 7C). The remaining 2 subjects (V.1 and VI.2), both of whom had early bilateral symptomatic involvement with small bilateral central scotomata, had responses with latencies in the normal range, but one (VI.2) had an increased inter-ocular latency difference.

Serial observations. In 6 affected subjects a second clinical and VEP examination was carried out after intervals of thirteen to fifteen months (Table 2). In Case V.10 who initially had only right-sided visual impairment of twelve years' standing, the initial VEP examination showed a normal response from the unaffected eye and a response which was delayed and markedly reduced in amplitude from the affected

FIG. 6. Fundus photograph of A, the right eye and B, fluorescein angiogram of the left eye showing tortuosity of small and medium-sized retinal vessels in Case VI.15, a 16-year-old boy with severe bilateral visual impairment and optic atrophy.



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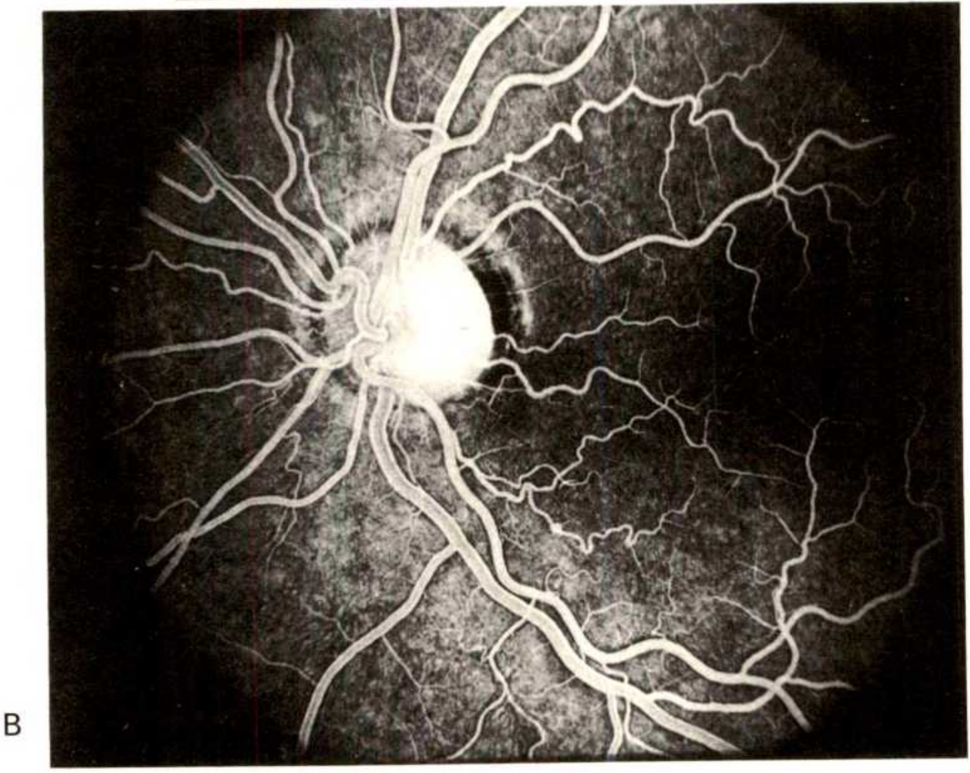

B

TABLE 1. SUMMARY OF NEURO-OPHTHALMIC AND VISUAL EVOKED POTENTIAL (VEP) FINDINGS IN THE 14 CLINICALLY AFFECTED SUBJECTS STUDIED

Case	*Age (yrs)*	*Sex*	*Visual acuity*	*Colour** vision*	*Visual fields*	*Optic discs*	*Vessel nos.‡*	*Vessel*** tortuosity*	*VEP*
III.13	81	F	R NPL	—	—	OA	5	0	Absent
			L NPL	—	—	OA	6	0	Absent
III.14	78	F	R CF	—	CS	OA	6	0	Absent
			L CF	—	CS	OA	4	0	Absent
IV.1*	46	M	R PPL	—	CS	OA	6	0	Absent
			L PPL	—	CS	OA	4	0	Absent
IV.4*	67	F	R PPL	—	CS	OA	5	1	Absent
			L PPL	—	CS	OA	4	1	Absent
IV.12§	50	M	R CF	—	CS	TP	4	0	Absent
			L CF	—	CS	Normal†	5	0	Absent
V.1*	40	F	R 6/5	—	Paracentral scotoma	TP	7	1	Normal
			L 6/5	0	CS	TP	9	1	Normal
V.10§	42	F	R 6/12	—	Small CS	TP	5	2	Delayed, low ampl.
			L 6/6	0	Normal	Normal	9	2	Normal
V.14§	34	M	R 6/18	4	Normal	TP	5	2	Absent
			L 6/24	5	Normal	TP	5	2	Absent
VI.2*	13	M	R 6/6	3	Relative CS	TP	6	1	Relative delay
			L 6/24	2	Relative CS	TP	6	1	Normal
VI.6	20	M	R 6/36	—	CS	OA	5	1	Absent
			L 6/60	—	CS	OA	4	2	Absent
VI.7	18	M	R 6/60	4	CS	OA	8	2	Absent
			L PPL	—	CS	OA	3	2	Absent
VI.8	19	M	R 6/6	0	Normal	Normal	10	3	Normal latency, broadened
			L 6/36	—	CS	TP	8	3	Absent
VI.14§	13	M	R 6/12	2	Relative CS	TP	9	2	Delayed, low ampl.
			L 6/9	3	Normal	TP	7	2	Delayed, bifid P2
VI.15§	16	M	R CF	—	CS	OA	4	1	Absent
			L CF	—	CS	OA	5	1	Absent

* VEP recorded with wide-field stimulation. ** Number of errors in reading Ishihara plates (0–7). *** Peripheral retinal vessel tortuosity graded from 0 (normal) to 4 (marked). † Papillo-macular bundle atrophy. ‡ *See* text. § Second examination. NPL No perception of light. PPL Peripheral perception of light only. CF Counting fingers only. CS Absolute central scotoma. OA Optic atrophy. TP Temporal pallor.

eye (fig. 7B). The second examination fourteen months later showed no significant change in the clinical or VEP findings. In Case VI.14 who had well-established bilateral visual involvement, the initial examination showed more or less symmetrically delayed and broadened responses. The follow-up examination fifteen months later showed no significant change in visual acuity, but the VEPs from both eyes were of lower amplitude, showed greater delays, and were broadened (fig. 7A). Case VI.8 had left monocular involvement from the age of 5 years with no recognizable VEP from the left eye and a widened response with a normal latency from the right eye (fig. 7C). No clinical or VEP change was found after an interval of fourteen months. Case IV.12 had normal visual acuity in both eyes when first seen. Two years later he suffered sudden loss of vision in the right eye, and the VEP from that eye was absent while that from the left eye was normal (fig. 7D).

TABLE 2. SUMMARY OF CLINICAL AND VISUAL EVOKED POTENTIAL (VEP) FINDINGS IN THE 6 CASES WHO WERE STUDIED ON TWO OCCASIONS

Case	Age (yrs)	Sex	Interval (months)		First examination		Second examination	
					Clinical findings	*VEP*	*Clinical findings*	*VEP*
IV.12†	50	M	14	R	VA 2/60, CS*	Absent	VA, CF, no CV; TP, CS	Absent
				L	VA 6/5*	Normal	VA, CF, no CV; CS papillo-macular bundle atrophy	Absent
V 10	42	F	13	R	VA 6/12*	Delayed, low ampl.	VA 6/12, no CV; TP, CS	No change
				L	VA 6/6*	Normal	VA 6/6, normal CV and disc	Normal
V.14	34	M	15	R	VA 6/18, no CS*	Absent	VA 6/18, impaired CV, TP, no CS	Absent
				L	VA 6/60, no CS*	Absent	VA 6/24, impaired CV, no CS	Absent
VI.8	19	M	14	R	VA 6/6, normal CV and disc, tortuous vessels	Normal latency, broad	No change	No change
				L	VA 6/36, no CV; CS, TP, tortuous vessels	Absent	No change	Absent
VI.14	13	M	14	R	VA 6/9*	P2 widened and delayed	VA 6/12, impaired CV rel CS, TP	Low ampl., increased delay, widened
				L	VA 6/9*	P2 widened and delayed	VA 6/9, impaired CV, TP	Bifid, low ampl., delayed P2
VI.15	16	M	14	R	VA, CF, CS*	Absent	VA, CF, no CV; CS, OA	Absent
				L	VA, CF, CS*	Absent	VA, CF, no CV; CS, OA	Absent

* No other information available. CF Counting fingers. CV Colour vision. † An examination two years previously had shown normal vision. CS Central scotoma. TP Temporal pallor. OA Optic atrophy. VA Visual acuity.

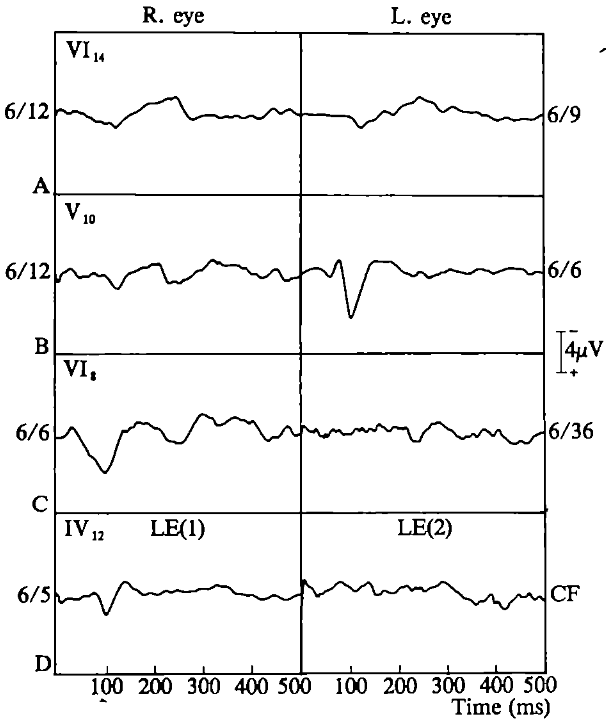

FIG. 7. Visual evoked potential recordings (retraced) from 4 affected subjects, each of whom was studied on two occasions. The visual acuities at the time of recording are also shown.

A, second examination in Case VI.14, a 13-year-old male with binocular involvement, showing responses which are reduced in amplitude, widened and delayed (P2 latency 120 ms for the right eye, 128 ms for the left eye; normal 85–113 ms); B, first examination in Case V.10, a 43-year-old female with right monocular involvement only. The response from the right eye is reduced in amplitude, widened and delayed (P2 latency 134 ms) while that from the left eye is normal (P2 latency 108 ms); C, 19-year-old male with left monocular involvement only (Case VI.8) in whom clinical and VEP findings remained unchanged over an interval of fourteen months. The response from the right eye is unduly widened but has a normal P2 latency (102 ms). The response from the left eye is grossly abnormal with no readily identifiable sub-components; D, left eye response recorded on two occasions fourteen months apart in a 50-year-old male (Case IV.12). At the time of the first examination the right eye only was clinically involved and the VEP from that eye was completely absent while that from the left eye (LE 1) was normal (P2 latency 102 ms). The second examination was performed after he had developed severe visual impairment in the left eye also (visual acuity reduced to counting fingers) and the left eye response was no longer identifiable (LE 2).

Within twelve months he had lost vision in the left eye, and a second VEP examination showed no identifiable response on either side. In two further subjects (V.14 and VI.15) with advanced bilateral visual impairment who had VEP studies on two occasions, no identifiable responses were present on either occasion.

Asymptomatic Subjects

One or more clinical abnormalities and/or an abnormal or atypical VEP were found in 16 of the 40 asymptomatic subjects studied (fig. 1; Table 3). Mild clinical

TABLE 3. SUMMARY OF CLINICAL AND VISUAL EVOKED POTENTIAL (VEP) ABNORMALITIES IN 16 ASYMPTOMATIC FAMILY MEMBERS

				Clinical abnormalities					
Case	*Age (yrs)*	*Sex*	*Potential risk of overt disease****	*Errors in colour vision (0–7)**	*Reduced vessels at disc margin (< 6)*	*Retinal vessel tortuosity (0–4)*	*Temporal pallor of optic disc*	*Relative central scotoma*	*VEP findings***
VI.9	16	M	+	—	5 (R, L)	4 (R, L)	—	—	Bifid P2
VI.10	12	M	+	—	—	2 (R) 3 (L)	—	—	
V.23	6	F	—	—	4 (R)	2 (R) 3 (L)	—	—	
V.22	9	F	—	—	—	—	—	—	
V.18	24	M	—	1 (R)	—	—	—	—	
VI.18	8	F	—	—	—	—	—	—	
V.2	25	M	+	1 (R)	—	2 (L)	—	—	Increased temporal dispersion
V.8	24	M	+	2 (L)	—	2 (L)	—	—	
VI.12	7	M	+	2 (R)	—	2 (R, L)	—	—	
VI.16	7	M	—	1 (R)	—	—	—	—	
IV.9	59	F	+	2 (L)	—	—	—	—	Delayed P2
IV.11	63	F	+	1 (R)	5 (R)	—	—	—	
VI.1†	15	F	+	1 (L)	—	2 (R, L)	—	(L)	Normal
VI.11	7	M	+	—	—	3 (R, L)	—	—	
V.11‡	37	F	+	—	5 (L)	1 (L)	(L)	—	
V.24	17	M	—	2 (R)	—	—	—	—	

* No. of errors in reading Ishihara plates. ** Bilateral in all cases except VI.10 who had only a R-sided abnormality. *** Descendants from the female lineage (who are at risk of developing the disease) are designated by + and those from male lineages as — in column 4. † The only case examined with wide-field (15 degrees radius) stimulation. ‡ Serial VEP examinations normal.

abnormalities comprising one or more error in identifying the Ishihara plates, undue pallor of the optic disc or reduced numbers of small vessels on the disc, excessive tortuosity of the retinal vessels (fig. 8), or the presence of a small central scotoma, were found in 12 subjects. Although none interpreted more than two of the 7 Ishihara plates incorrectly, unlike the occasional normal subject who misinterpreted a plate, the Leber subjects were slower and were unable to correct their errors quickly. All 16 had corrected visual acuities of 6/9 or better.

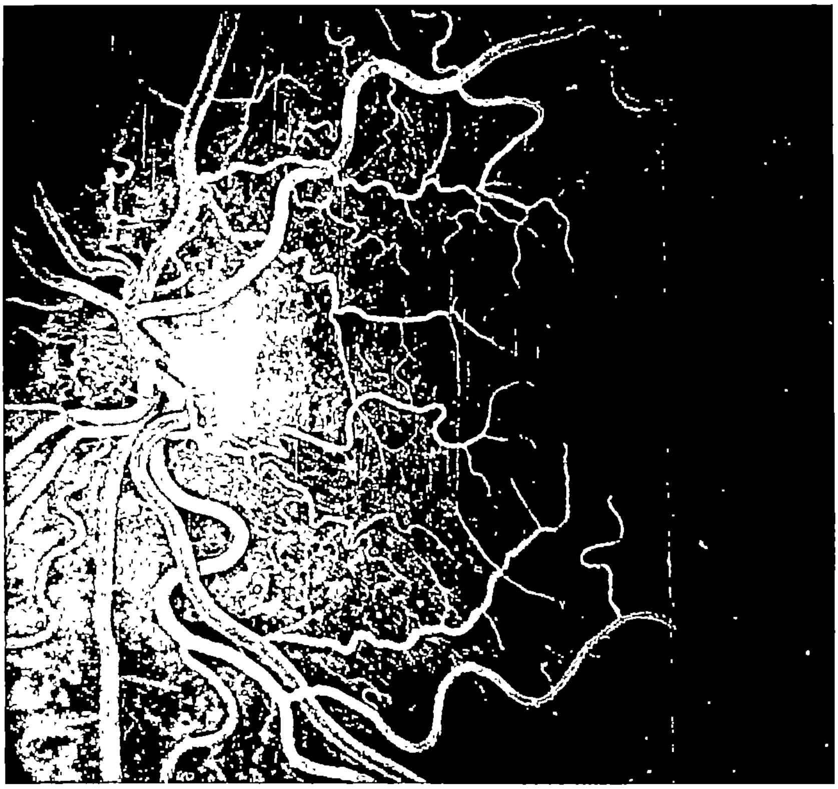

FIG. 8. Fundus photograph of early fluorescein angiogram from a 16-year-old asymptomatic male (VI.9) from a female line showing prominent tortuosity of the retinal vasculature. (Reprinted with the permission of Dr J. A. Rogers and the Royal Australian College of Ophthalmologists).

The VEP was mildly abnormal or showed atypical features in 12 of the 16 subjects including 4 with no clinical abnormality, and was normal in 4 subjects with mild clinical abnormalities (Table 3). VEP changes were of three types. Six subjects showed a bifid P2 component (bilateral in 5 and unilateral in Case VI.10) which was also abnormally widened in 5 (fig. 9). Only 2 of these subjects (VI.9 and VI.10) were from the female lineage and at risk of developing the disease, the other 4 being from male lineages. In 4 subjects, VEP latencies were normal but the responses showed increased temporal dispersion. All 4 were males, 3 being from the female lineage and at risk. Finally, 2 females from the female lineage (IV.9 and IV.11) showed responses with latencies just above the upper limit of normal. The detailed form of VEP examination with 3 degrees radius central field stimulation was carried out in 15 of the 16 subjects. In the remaining subject (VI.1), who had a small relative central scotoma in the left eye, only the wide-field (15 degrees radius) stimulation was performed, and the VEP latency was found to be normal for both eyes.

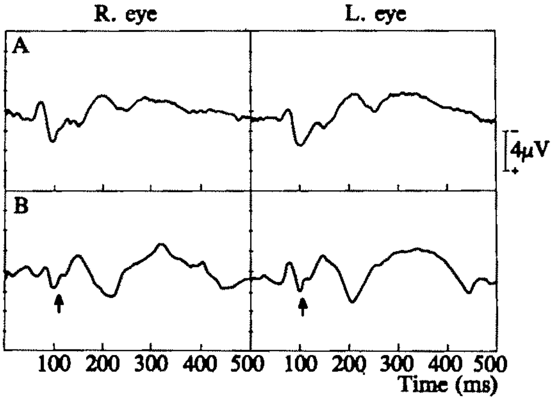

FIG. 9. Visual evoked potentials from both eyes of A, a 24-year-old male from a male line (V.18) and B, of a 16-year-old male from a female line (VI.9) showing the bifid P2 component of the response (arrows).

The 21 subjects from the female lineage who were at risk comprised 12 males and 9 females. Of the 12 males, 5 showed asymptomatic clinical and VEP abnormalities, and one showed only a clinical abnormality. Two of the 9 females at risk of developing or transmitting the disease had both clinical and VEP abnormalities, and 2 others showed only clinical abnormalities. Thus, asymptomatic abnormalities were found in 10 of the 21 subjects at risk of developing the disease (50 per cent) and in 6 of the 19 (30 per cent) who were derived from male lineages and not at risk.

Thirty of the 54 members of the family examined were females. Of these females 9 were obligate carriers and 5 were potential carriers (fig. 1; Table 4). Obligate carriers were defined as females who either had symptomatic disease themselves or who had children with the disease. Potential carriers were asymptomatic females of female lineage who had only asymptomatic children or who were childless. Five of the 9 obligate carriers had the disease themselves. Two of the 4 who were unaffected had asymptomatic clinical and/or VEP abnormalities. Only 2 of the 5 potential carriers (V.5 and V.9) could not be closely identified with the disease. V.5 had only one young son and neither she nor her son showed asymptomatic abnormalities, while V.9, who was childless, also showed no abnormalities. Of the remaining 3, IV.9 and V.12 had sons with asymptomatic abnormalities, IV.9 herself

TABLE 4. SUMMARY OF FINDINGS IN OBLIGATE AND POTENTIAL FEMALE CARRIERS AND THEIR OFFSPRING

	Carriers			*Offspring*		
	Age (yrs)	*Clinically affected*	*Asymptomatic* abnormalities*	*No. of children*	*Clinically affected*	*Asymptomatic* abnormalities*
Obligate carriers						
III.13	81	+	—	4M	1M	—
III.14	78	+	—	0	—	—
IV.4	67	+	—	0	—	—
IV.10	62	—	—	3F	1F	1F
IV.11	63	—	+	1M, 1F	1M	—
V.1	40	+	—	1M, 1F	1M	1F
V.10	42	+	—	2M	2M	—
V.11	37	—	+	4M	1M	3M
V.13	39	—	—	2M	2M	—
Potential carriers						
IV.9	59	—	+	3M, 2F	—	2M
V.5	41	—	—	1M	—	—
V.9	21	—	—	0	—	—
V.12	31	—	—	1M, 1F**	—	1M
VI.1	15	—	+	0	—	—
Total		5	4	27	9	8

* *See* text. ** Not examined. F = female. M = male.

having similar findings, while VI.1 who was 15 years old and childless had asymptomatic clinical abnormalities. Thus, 12/14 (86 per cent) females derived from the female lineage could be classified as carriers, either they or their offspring having evidence of overt or asymptomatic disease.

Neurological Examination

No other abnormalities were found in the 54 clinically affected or asymptomatic family members examined.

DISCUSSION

Affected Subjects

Neuro-ophthalmic findings. The diagnosis of Leber's optic neuropathy in the present family was based upon the characteristic pattern of inheritance with predominant involvement of males, and the typical acute or subacute sequential loss of vision in affected subjects. This was bilateral in all but 2 cases (V.10 and VI.8) who have had purely monocular involvement for twelve and fourteen years, respectively, an unusual occurrence as most cases previously described in the literature have developed loss of vision in the second eye within twelve months of the first (Went, 1972). The almost invariable finding of reduced visual acuity, of central scotomata, and of severe impairment of colour vision in the present cases reflect the known predilection of the disease process for the central portions of the optic nerves. The retinal degeneration which was found in 2 elderly female members of this family with an otherwise typical history of Leber's optic neuropathy is probably unrelated as we have not found reference to this association in any of the large series reported in the literature.

The peripapillary telangiectasia and swelling of the optic disc which have been reported by others in the acute phases of the disease (Smith, Hoyt and Susac, 1973; Nikoskelainen, Sogg, Rosenthal, Friberg and Dorfman, 1977) were not seen in any of our 14 affected subjects all of whom were studied months or years after the onset of visual impairment. On the other hand, tortuosity of the more peripheral retinal vessels, which has also been noted in the early stages of the disease (Smith *et al.*, 1973; Nikoskelainen *et al.*, 1977), was observed in 5 of the 14 cases. It was a prominent feature not only in the affected eye but also in the asymptomatic eye of Case VI.8 and was also noted in a number of the asymptomatic family members. The significance of this finding is uncertain. It has been suggested that it may represent a separately inherited trait (Rogers, 1977), but further genetic studies are required to determine whether or not this is so.

Visual evoked potential findings. The VEP findings have been described in detail in only two previous cases of Leber's optic neuropathy who were first studied in the acute phase of the disease (Dorfman, Nikoskelainen, Rosenthal and Sogg, 1977). In this study prolongation of the response latency and ultimately complete loss of the response were reported. The present findings in a larger group of subjects with established disease illustrate the spectrum of abnormalities which may be found in cases with variable degrees of visual impairment, and allow certain observations to be made regarding the pathogenesis of the optic neuropathy.

While in cases with advanced visual impairment there was no identifiable VEP, a recognizable response was found in cases with less severe involvement and visual acuities of 6/36 or better. In such cases the VEP was characteristically reduced in size, desynchronized and delayed. By comparison with the usual findings in patients with demyelinating optic neuropathy (Halliday and McDonald, 1977), the responses in these cases were in general less delayed but were more markedly reduced in amplitude and disorganized, implying a more severe disturbance of conduction in the optic nerve in Leber's disease, which would be in keeping with extensive demyelination with associated loss of nerve fibres. Whether or not the lesion is initially a selectively demyelinating one remains to be determined. Sequential studies of further cases seen in the acute phases of the disease should throw further light upon this point.

Three further points of difference from the findings in patients with demyelinating optic neuropathy are worthy of comment. First, in contrast to the situation in such patients, none of the present Leber patients showed any significant recovery of vision, and sequential VEPs showed deterioration rather than improvement. Secondly, although abnormalities of the VEP were found in some asymptomatic eyes in patients with monocular involvement, and in some of the asymptomatic subjects described here, these were less marked than the subclinical abnormalities which are found in some patients with multiple sclerosis (Halliday and McDonald, 1977). Thirdly, the finding of a normal VEP in some patients with symptomatic and clinically overt optic nerve involvement is rare in patients with demyelinating optic neuropathy. Both the patients in this latter category were studied using only wide-field stimulation, and it is possible that the use of central-field or foveal stimulation might have disclosed an abnormality in these cases (Hennerici, Wenzel and Freund, 1977).

Subclinical involvement. Subclinical abnormalities were sought in the unaffected eye of those cases with purely monocular involvement (IV.12, V.10, VI.8), and each of these cases had serial clinical and VEP assessments (Table 2). In Case IV.12, who eventually developed the typical bilateral visual failure, clinical and VEP examination failed to reveal any abnormalities in the asymptomatic eye prior to the development of binocular blindness. In Case V.10, who was an obligate carrier with monocular involvement of many years standing, no clinical or VEP abnormality was found in the asymptomatic eye and no change had occurred after an interval of thirteen months. On the other hand, in Case VI.8, who had also had purely monocular involvement for many years, excessive vessel tortuosity and desynchronization of the VEP were found in the asymptomatic eye, with no significant change over a fourteen-month period. The changes found in this case were similar to those found in a proportion of the asymptomatic family members studied. The variable findings and clinical course in these 3 cases suggest that there is a spectrum of involvement, ranging from the typical severe bilateral optic neuropathy on the one hand (IV.12) to an entirely monocular form of the disease on the other (V.10), and which includes limited forms of expression of the disease in some cases (VI.8).

Conclusions. The present clinical and VEP findings in affected subjects raise a number of points of importance. First, the finding of central scotomata, temporal pallor of the optic discs, dyschromatopsia and reduced visual acuity, particularly in an adolescent or young adult male, should suggest the possibility of Leber's optic neuropathy. Secondly, the presence of purely monocular symptoms for long periods is not inconsistent with this diagnosis. Thirdly, the finding of subclinical abnormalities in the asymptomatic eye in cases of unilateral optic neuropathy in whom an inadequate family history is obtained would support the diagnosis, and may allow invasive forms of investigation to be deferred. Lastly, the VEP changes in symptomatic cases of Leber's disease show certain differences from those found in typical cases of demyelinating optic neuropathy, in keeping with combined demyelination and loss of nerve fibres in the optic nerve.

Asymptomatic Subjects

The finding of subclinical abnormalities in some males at risk, and in obligate or potential female carriers, suggests that preclinical diagnosis and definition of carrier status may be possible in Leber's disease by combining a detailed neuro-ophthalmic examination and VEP analysis. Moreover, the finding of similar abnormalities in some descendants from male lineages suggests the possibility of transmission of a partial form of the disease by males.

In view of the subtle nature of the abnormalities found in these cases, it is important to consider the validity of the criteria employed. Impairment of colour vision is a sensitive index of damage to the optic nerve (Walsh and Hoyt, 1969). The degree of impairment found in the Leber subjects was mild but was considered to be significant as it was outside our established limits of normality. Similarly, the reduced retinal vessel counts recorded in some subjects were thought to be significant and to reflect some involvement of the optic nerve. Excessive tortuosity of retinal vessels was observed in some of the clinically-affected patients in the present study and has also been noted previously (Smith *et al.*, 1973; Nikoskelainen *et al.*, 1977). Although this change is difficult to quantify, the degree of tortuosity was also considered to be excessive in 9 of the present asymptomatic subjects. It may be that more sensitive tests of colour vision such as the 100-hue test (Farnsworth-Munsell) and quantitative analysis of the central field would prove of greater value in detecting early involvement of the optic nerve in these subjects. For logistic reasons such techniques could not be used in the present study.

The criteria upon which the VEP was classified as abnormal in 12 of the 40 subjects were delay or widening of the response, or an atypical bifid response. There is good evidence to associate a delayed response with a predominantly demyelinating process (Halliday and McDonald, 1977), while increased width of the response, indicating temporal dispersion of the afferent volley, has also been found in some patients with early multiple sclerosis with a normal response latency (Collins *et al.*, 1978).

The significance of the atypical bifid positivity found in 6 of the 40 subjects is less certain. A similar appearance has been noted previously in 2 asymptomatic members of a Leber sibship, one of whom had dyschromatopsia and similar ophthalmoscopic changes to those described here (Dorfman *et al.*, 1977). Although this VEP appearance is occasionally seen in midline recordings from normal subjects, in our experience it has been a very uncommon finding, both in adults and in children, when using 3 degrees radius central field stimulation. Using vertical half-field stimulation and multi-channel recording Blumhardt, Barrett, Halliday and Kriss (1978) showed that the components recorded in the contralateral occipital channels can influence the configuration of the midline response in some normal subjects, but that this is less likely to occur when central field stimulation is used, as the lateral components are then attenuated. The presence of a scotoma may also result in a bifid positive response in the midline channel due to relative attenuation of the central response and augmentation of the lateral components (Blumhardt *et al.*, 1978). Another possible explanation for this finding is the arrival of two afferent volleys at the cortex for each stimulus due to the existence of two populations of fibres conducting at different velocities in the visual pathway. Further studies using half-field stimulation and multi-channel recording of the VEP are required to elucidate the significance of this finding in this group of subjects.

The significance of the subclinical abnormalities found in some asymptomatic subjects in the present study is uncertain. Sequential studies will be necessary to determine whether the minor changes found in cases at risk are forerunners of the more severe optic nerve damage which results in visual impairment, or whether they represent a mild nonprogressive form of the disease. Similarly, serial examinations will help to determine the natural history of the minor abnormalities found in 30 per cent of descendants from male lineages who are theoretically not at risk of developing visual failure.

A carrier rate approaching 100 per cent has been postulated previously in the daughters of female carriers of Leber's disease (Seedorf, 1970). With the present techniques a high carrier rate (86 per cent) has been confirmed in a family spanning only 4 generations, whereas with the usual methods of pedigree analysis this has previously only been established with studies of very large families with brisk rates of reproduction (Seedorf, 1970). Although the techniques used in this study showed abnormalities in a proportion of known carriers of the disease, in some carriers no abnormality was found either with careful neuro-ophthalmic examination or analysis of the VEP. Even the combined application of these procedures does not therefore provide a reliable method for prediction of carrier status in the individual female. Whether the additional use of other procedures such as more discriminating tests of colour vision, and quantitative central field analysis will allow a higher proportion of carriers to be identified remains to be determined. Nevertheless, the finding of such a high carrier frequency in the present family has allowed a more confident approach to genetic counselling.

The finding of asymptomatic abnormalities in 30 per cent of descendants from male lineages in the present family is of interest in relationship to hypotheses regarding the method of transmission of Leber's disease. With the knowledge that familial neurological diseases such as kuru and Creutzfeld-Jacob disease can be due to vertical transmission of a presumed viral agent (Gajdusek and Gibbs, 1975) it is tempting to consider a similar mechanism in Leber's optic neuropathy with its unique familial distribution. Placental transfer of a viral agent (Erikson, 1972; Harper, 1977) could explain many of the features of the heredity of the disease but would not account for the relatively constant ratio of affected and unaffected females, or for the fact that not all sons develop the disease, unless some form of sex-limited resistance is invoked. Cytoplasmic transfer, a postulated mechanism of transmission of an 'agent' in the non-nuclear substance of the ovum, could account for some of the hereditary features of the disease and for the present observations. If a critical quantity of such an 'agent' is required, this might explain the failure of males to transmit the overt form of the disease, as only about 1 per cent of the cytoplasm of the zygote is thought to be derived from the spermatozoon (Fine, 1977). Moreover, if the quantity of the 'agent' was transmitted in this proportion, incomplete forms of the disease might reasonably be expected in descendants from male lineages. The finding that mammalian spermatozoa can transmit virus DNA to the ovum is of interest in this regard (Brackett, Baranska, Sawicki and Koprowski, 1971). The possibility of mitochondrial inheritance (Fine, 1978) should be especially considered, as such a mechanism could account for female transmission of the overt form of the disease, for phenotypic gradations in affected individuals, and for transmission of partial forms of the disease by males.

SUMMARY

Fourteen clinically affected and 40 asymptomatic members of a six generation family with Leber's optic neuropathy have been studied clinically and by recording pattern-reversal visual evoked potentials. While 12 of the affected members had suffered the typical sequential bilateral failure of vision, in 2 the condition was still monocular after periods of 12 and 14 years. Reduced vascularity of the optic nerve head was found in 11 of these cases, all of whom had some degree of optic atrophy, and showed a significant correlation with the visual acuity. Excessive tortuosity of peripheral retinal vessels was noted in 6 cases and was a prominent feature in the unaffected eye of one of the subjects with monocular visual impairment. In cases with advanced visual impairment the VEP was absent bilaterally, while in those with less severe involvement responses which were delayed, desynchronized and much smaller than normal could still be recorded. Two subjects with early bilateral clinical involvement had normal or minimally abnormal responses. Repeat studies in 6 subjects after intervals of up to fifteen months showed no change in 4 and a deterioration in 2. It is concluded that the VEP findings in clinically affected subjects are in keeping with a severe demyelinating lesion of the optic nerve with associated nerve fibre loss.

Mild impairment of colour vision, pallor or reduced vascularity of the optic nerve head, excessive tortuosity of retinal vessels, a small central scotoma, and/or mild abnormalities or atypical features of the VEP were found in 16 of the 40 asymptomatic family members studied. Such abnormalities were present in 50 per cent of descendants from the female lineage who were at risk of developing the disease, and also in 30 per cent of descendants from male lineages who were not at risk. These findings suggest that there is a stage prior to the onset of visual impairment during which subtle abnormalities may be detected in individuals at risk of developing or transmitting the disease. The finding of asymptomatic abnormalities in descendants from male lineages could be accounted for by transmission of a partial form of the disease by affected or unaffected males, which would be in accord with a cytoplasmic mechanism of transmission for the disease.

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REFERENCES

ADAMS, J. H., BLACKWOOD, W. and WILSON, J. (1966) Further clinical and pathological observations on Leber's optic atrophy. *Brain*, **89**, 15–26.

BLUMHARDT, L. D., BARRETT, G., HALLIDAY, A. M. and KRISS, A. (1978) The effect of experimental 'scotomata' on the ipsilateral and contralateral responses to pattern-reversal in one half-field. *Electroencephalography and Clinical Neurophysiology*, **45**, 376–392.

BRACKETT, B. G., BARANSKA, W., SAWICKI, W. and KOPROWSKI, H. (1971) Uptake of heterologous genome by mammalian spermatozoa and its transfer to ova through fertilisation. *Proceedings of the National Academy of Science, USA*, **68**, 353–357.

COLENBRANDER, M. C. (1962) Observations on the heredity of Leber's disease. *Ophthalmologica*, **144**, 446–450.

COLLINS, D. W. K., BLACK, J. L. and MASTAGLIA, F. L. (1978) Pattern-reversal visual evoked potential. Method of analysis and results in multiple sclerosis. *Journal of the Neurological Sciences*, **36**, 83–95.

DORFMAN, L. J., NIKOSKELAINEN, E., ROSENTHAL, A. R. and SOGG, R. L. (1977) Visual evoked potentials in Leber's hereditary optic neuropathy. *Annals of Neurology*, **1**, 565–568.

ERIKSON, R. P. (1972) Leber's optic atrophy, a possible example of maternal inheritance. *American Journal of Human Genetics*, **24**, 348–349.

FINE, P. E. M. (1977) Analysis of family history data for evidence of non-Mendelian inheritance resulting from vertical transmission. *Journal of Medical Genetics*, **14**, 399–407.

—— (1978) Mitochondrial inheritance and disease. *Lancet*, **ii**, 659–661.

GAJDUSEK, D. C. and GIBBS, C. J. Jr. (1975) Familial and sporadic chronic neurological degenerative disorders transmitted from man to primates. In: *Primate Models of Neurological Disorders*. Edited by B. S. Meldrum and C. D. Marsden. New York: Raven Press, pp. 219–317.

HALLIDAY, A. M. and McDONALD, W. I. (1977) Pathophysiology of demyelinating disease. *British Medical Bulletin*, **33**, 21–27.

HARPER, P. S. (1977) Mendelian inheritance or transmissable agent? The lesson of Kuru and the Australia antigen. *Journal of Medical Genetics*, **14**, 389–398.

HENNERICI, M., WENZEL, D. and FREUND, H.-J. (1977) The comparison of small-size rectangle and checkerboard stimulation for the evaluation of delayed visual evoked responses in patients suspected of multiple sclerosis. *Brain*, **100**, 119–136.

IMAI, Y. and MORIWAKI, D. (1936) A probable case of cytoplasmic inheritance in man; a critique of Leber's disease. *Journal of Genetics*, **33**, 163–167.

KWITTKEN, J. and BAREST, H. D. (1958) The neuropathology of hereditary optic atrophy (Leber's disease): the first complete anatomic study. *American Journal of Pathology*, **34**, 185-207.

LEBER, T. (1871) Über hereditäre und congenitalangelegte Sehnervenleiden. *Albrecht von Graefes Archiv für Ophthalmologie*, **2**, 249-291.

LEES, F., MACDONALD, A. M. E. and TURNER, J. W. A. (1964) Leber's disease with symptoms resembling disseminated sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 415-421.

LUNDSGAARD, R. (1944) Leber's disease: A genealogic, genetic and clinical study of 101 cases of retrobulbar optic neuritis in 20 Danish families. *Acta Ophthalmologica, Copenhagen*, Suppl. **21**, 300-306.

MCLEOD, J. G., LOW, P. A. and MORGAN, J. A. (1978) A family with Charcot-Marie-Tooth disease and Leber optic atrophy. *Neurology, Minneapolis*, **28**, 179-184.

MORLET, C. (1921) Hereditary optic atrophy a possible menace to the community. *Medical Journal of Australia*, **11**, 499-502.

NIKOSKELAINEN, E., SOGG, R. L., ROSENTHAL, A. R., FRIBERG, T. R. and DORFMAN, L. J. (1977) The early phase in Leber hereditary optic atrophy. *Archives of Ophthalmology*, **95**, 969-978.

OUD, J. S. F., HENNEMAN, I. P., BRUGGE, R. J., HARIGA, J. and MARTIN, J. J. (1968) La maladie de Leber etudie anatomique de deux cas dans une fratrie. *Journal of the Neurological Sciences*, **6**, 401-417.

REHSTEINER, K. (1930) Die erste anatomische Untersuchung eines Falles von geschlechtsgebunden-hereditärer Sehnervenatrophie (Leberscher Krankheit). *Albrecht von Graefes Archiv für Ophthalmologie*, **125**, 14-28.

ROGERS, J. A. (1977) Leber's disease. *Australian Journal of Ophthalmology*, **5**, 111-119.

RØNNE, H. (1944) The inheritance of Leber's disease. *Acta Ophthalmologica, Copenhagen*, **22**, 203-214.

SEEDORF, T. (1968*a*) Leber's disease. *Acta Ophthalmologica, Copenhagen*, **46**, 4-25.

—— (1968*b*) Leber's disease. *Acta Ophthalmologica, Copenhagen*, **46**, 985-992.

—— (1969*a*) Leber's disease. *Acta Ophthalmologica, Copenhagen*, **47**, 23-29.

—— (1969*b*) Leber's disease. *Acta Ophthalmologica, Copenhagen*, **47**, 813-821.

—— (1970) Leber's disease. *Acta Ophthalmologica, Copenhagen*, **48**, 187-213.

SMITH, J. L., HOYT, W. F. and SUSAC, J. O. (1973) Ocular fundus in acute Leber optic neuropathy. *Archives of Ophthalmology*, **90**, 349-354.

VAN SENUS, A. H. C. (1963) Leber's disease in the Netherlands. *Documenta Ophthalmologica*, **17**, 1-162.

VEITH, N. W. and SACKS, J. G. (1973) Enumeration of small vessels on the optic discs in normal eyes. *American Journal of Ophthalmology*, **76**, 660-661.

WAARDENBERG, P. J. (1969) Some remarks on the clinical and genetic puzzle of Leber's optic neuritis. *Journal of Human Genetics*, **17**, 479-496.

WALLACE, D. C. (1970) A new manifestation of Leber's disease and a new explanation for the agency responsible for its unusual pattern of inheritance. *Brain*, **93**, 121-132.

WALSH, F. B. and HOYT, W. F. (1969) *Clinical Neuro-ophthalmology*. 3rd Edition. Vol. 1. Baltimore: Williams and Wilkins, pp. 870.

WENT, L. N. (1972) Leber disease and variants. In: *Handbook of Clinical Neurology*. Vol. 13. Edited by P. J. Vynken and G. W. Bruyn. New York: American Elsevier Press, pp. 94–110.

WILSON, J. (1963) Leber's hereditary optic atrophy—some clinical and ætiological considerations. *Brain*, **96,** 347–362.

—— (1965) Leber's hereditary optic atrophy: A possible defect of cyanide metabolism. *Clinical Science and Molecular Medicine*, **29,** 505–515.

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Brain (1979), **102**, 581–594

CENTRAL CORE DISEASE

CLINICAL AND PATHOLOGICAL EVIDENCE OF PROGRESSION WITHIN A FAMILY

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INTRODUCTION

CENTRAL cores within muscle fibres were first described by Shy and Magee (1956) when they reported 5 members from 3 generations of a family, who all had a congenital and non-progressive myopathy. Central cores have since been found in association with malignant hyperpyrexia (Denborough, Dennett and Anderson, 1973) and progressive pes cavus, and in a family whose primary disability was muscle cramps (Bethlem, Van Gool, Hülsmann and Meijer, 1966). Structures resembling central cores have also been demonstrated in experimental animals following tenotomy (Shafiq, Gorycki, Asiedu and Milhorat, 1969) and during reinnervation (Dubowitz, 1967). Most reported cases, however, have been of a congenital and non-progressive myopathy similar to the original cases of Shy and Magee. A single case of myopathy apparently starting in later life has been described (Dubowitz and Platts, 1965) but interpretation was complicated by co-existing renal failure.

A family is described in which central core disease presented as late-onset progressive muscle weakness in one member, and as a congenital non-progressive myopathy in others.

CASE HISTORIES

Case 1, R.H.

A 50-year-old plumber was referred in January 1977 with a twelve-month history of weakness in his legs. He had noticed difficulty in climbing stairs, preferring to mount them on all fours. Apart from intermittent back pain for eleven years there was no significant past history. The age at which he had first walked was not known, but as a young man he had had no difficulty in running and his athletic performance at school had been average. Family history, however, revealed that three of his sisters and his eldest daughter did not climb stairs normally.

Examination. He was an intelligent man of short stature (5′ 4″, 1.63 m). He had a slight lumbar scoliosis and pes cavus. There was mild weakness of both deltoids and triceps and he could not sit up unaided from the lying position or stand from squatting. There was no weakness of distal muscles or of those supplied by the cranial nerves. The left knee jerk was depressed but deep reflexes were otherwise normal. Plantar responses were flexor and sensation and co-ordination were normal.

Investigations. Hæmoglobin, white blood count, erythrocyte sedimentation rate (ESR), urea, sodium, potassium, calcium, chloride, bicarbonate, free thyroxine index and Wassermann reaction in blood and cerebrospinal fluid (CSF) were all within normal limits. CSF pressure was 130 mm of CSF, and protein, sugar and cell count of the fluid were normal. Electrocardiogram was normal. X-rays of chest and skull were normal. Lumbar spine x-ray showed scoliosis with sacralization of the fifth lumbar vertebra.

Creatine phosphokinase (CPK) was raised on two occasions at 565 and 730 IU/l (normal laboratory value up to 100 IU/l).

Electromyography of right biceps, triceps, deltoid, vastus lateralis and tibialis anterior muscles was performed. A mixture of normal motor units and short duration polyphasic units was obtained on recruitment. There was no spontaneous activity at rest and interference patterns were complete. The right ulnar, median and lateral popliteal nerves showed normal conduction velocities. Sensory nerve action potentials of the right ulnar and median nerves at the wrist were of normal amplitude.

A muscle biopsy was performed at that time and showed central core disease.

Over the following eighteen months he complained of progressive difficulty with heavy lifting which made it increasingly difficult for him to do his job as a plumber. His arms as well as his legs were affected and his symptoms were worse towards the end of the day. He was readmitted in July, 1978 when examination showed mild weakness of both deltoids, triceps, biceps and hip flexors, which was more obvious than at his previous admission. As before, he was unable to sit up unaided from the lying position, or to stand from squatting. Remaining neurological examination was normal. CPK was 710 IU/l. A repeat muscle biopsy was performed.

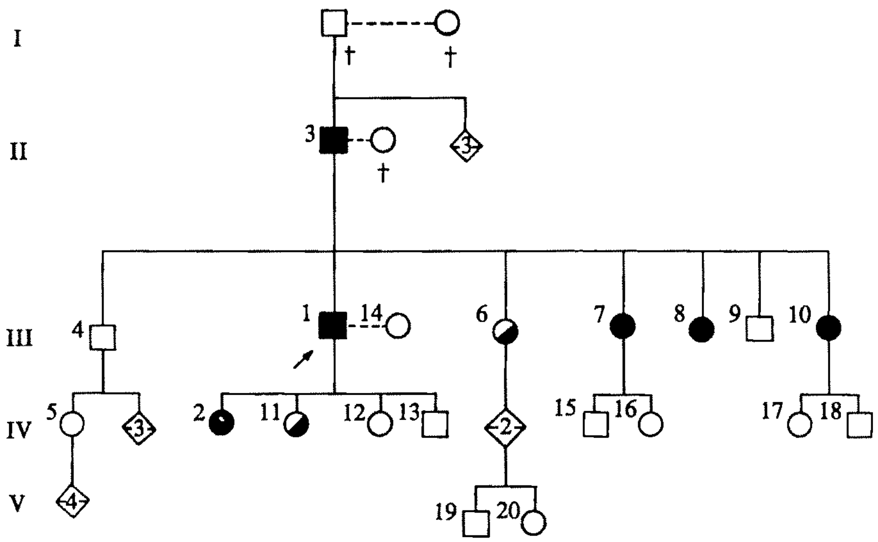

FIG. 1. The H family. Numbers at top left of symbols refer to Case numbers. ■ = muscle weakness. ◐ = raised CPK. □ = normal. ◇ = number of siblings not examined. † = dead. ↗ = propositus.

Case 2, L.H.

The eldest daughter of Case 1 was 20 years old, and when it became known that her father had an unusual muscle disease she agreed to investigation. She had been slow to sit up (1½ years) and to walk (2½ years). She had been poor at running, being consistently last in athletic events at school, and had always had difficulty climbing stairs. Her weakness was not getting worse.

Examination. She was a pleasant, short girl (4′ 5″, 1.35 m) of above average intelligence. There was a prominent lumbar lordosis and bilateral Achilles tendon shortening. There was mild weakness of both triceps muscles and of hip flexion. She could not sit up from a low chair unaided or rise from the supine position. Remaining power was normal, deep reflexes were normal, plantar responses flexor and sensation and co-ordination were intact.

Investigations. Hæmoglobin, white blood count, ESR, urea, sodium, potassium, calcium, chloride, bicarbonate, Wassermann reaction, skeletal muscle antibody and free thyroxine index were within normal limits. Karyotype was 46XX. X-ray of chest, skull and spine were normal. Electrocardiogram showed Wolff-Parkinson-White syndrome, Type A. CPK was 165 and 85 IU/l. Electromyography was similar to Case 1. Motor conduction velocities and sensory nerve action potentials at the wrist were normal for the right median and ulnar nerves.

FAMILY STUDIES

Eighteen other members of the family from four generations were seen and examined. Blood for CPK estimation was taken from ten of the adults but electromyography and muscle biopsy were not carried out. The family tree is shown in fig. 1, and details are summarized in Table 1.

TABLE 1. CLINICAL AND BIOCHEMICAL FEATURES OF THE H FAMILY

Case	*Age (yrs)*	*Sex*	*Muscle symptoms*	*Duration of symptoms*	*Muscle weakness*	*Musculo-skeletal abnormality*	*CPK (IU/l)*
1	50	M	+	1 yr	+	+	565*
2	20	F	+	18 yrs	+	+	165*
3	71	M	+	5 yrs	+	—	670*
4	53	M	—	—	—	—	60
5	33	F	—	—	—	—	—
6	47	F	—	—	—	—	470*
7	41	F	+	36 yrs	+	—	685*
8	40	F	+	35 yrs	+	+	235*
9	37	M	—	—	—	+	90
10	34	F	+	29 yrs	+	—	140*
11	18	F	—	—	—	+	750*
12	16	F	—	—	—	—	90
13	9	M	—	—	—	—	—
14	46	F	—	—	—	—	65
15	18	M	—	—	—	—	—
16	14	F	—	—	—	—	—
17	14	F	—	—	—	—	—
18	4	M	—	—	—	—	—
19	5	M	—	—	—	—	—
20	3	F	—	—	—	—	—

* Elevated CPK.

Case 3, G.H. Aged 71 Years. Father of Case 1

He had noticed difficulty climbing stairs for five years. There had been no neurological symptoms prior to this, and his athletic performance when young had been average.

Examination. He was short (5′ 4″, 1.63 m) with a lumbar lordosis. He was unable to sit up unaided from the supine position and walked with a waddling gait. The remaining examination was normal. CPK was elevated at 670 IU/l.

His father, who had died at the age of 87 years, had been Army cross-country champion and a part-time wrestler. His mother had died at 65 years of age but little was known about her. He had three brothers who were living abroad. His wife had died aged 69 years and had no symptoms of weakness during life.

Case 4, A.H. Aged 53 Years. Brother of Case 1

He had had no difficulty running or climbing stairs. Examination was entirely normal. CPK was 60 IU/l.

Case 5, B.H. Aged 33 Years. Daughter of Case 4

She had walked at 9 months of age and was asymptomatic. Examination was normal. She had three siblings and four children all of whom had walked between 9 and 12 months of age and whose motor development had been normal.

Case 6, J.H. Aged 47 Years. Sister of Case 1

She had never had difficulty running or climbing stairs. Examination was normal. CPK was elevated at 470 IU/l.

She had two children whose motor development had been normal and two grandchildren, F.H. aged 5 years (Case 19) and H.H. aged 3 years (Case 20) who had both walked at 1 year of age and who showed no clinical evidence of muscle weakness.

Case 7, D.H. Aged 41 Years. Sister of Case 1

She had climbed stairs on all fours for as long as she could remember. At school she had been unable to keep up with other girls. She coped easily with her duties as a housewife. Her symptoms were not deteriorating.

Examination. There was a mild weakness of hip flexors bilaterally and she was unable to rise from the squatting position. The remaining examination was normal. CPK was raised at 685 IU/l.

Her two children J.H. aged 18 years (Case 15) and N.H. aged 14 years (Case 16) were athletic and showed no weakness on examination.

Case 8, M.H. Aged 40 Years. Sister of Case 1

She had always had difficulty climbing stairs and had been very poor at running. Her symptoms were not getting worse. There was a lumbar scoliosis. Hip flexors were weak bilaterally and she could not sit up unaided from the supine position. CPK was raised at 235 IU/l.

Case 9, E.H. Aged 37 Years. Brother of Case 1

He had no symptoms of weakness and athletic performance at school had been normal. He had a lumbar kyphoscoliosis and mild pes cavus but there was no evidence of muscle weakness. CPK was 90 IU/l.

Case 10, V.H. Aged 34 Years. Sister of Case 1

She had always had difficulty climbing stairs and was poor at running. The symptoms had not got worse. There was mild weakness of triceps and hip flexors and she could not rise unaided from the supine position. Remaining examination was normal. CPK was elevated at 140 IU/l.

Her two children W.H. aged 14 years (Case 17) and P.H. aged 4 years (Case 18) had no symptoms or signs of weakness.

Case 11, T.H. Aged 18 Years. Daughter of Case 1

She had walked at 13 months of age, but had been treated for scoliosis as a child. She had no difficulty running or climbing stairs. There was an area of apparent muscle hypertrophy affecting the right hamstrings. No weakness was detectable. CPK was raised at 750 IU/l.

Case 12, K.H. Aged 16 Years. Daughter of Case 1

She had walked at 12 months of age and was athletic. There was no weakness. CPK was 90 IU/l.

Case 13, Y.H. Aged 9 Years. Son of Case 1

He had walked at 9 months of age and was athletic. There was no evidence of weakness.

Case 14, Z.H. Aged 46 Years. Wife of Case 1

She had no symptoms of weakness. She had had a stillbirth and three miscarriages in addition to four children. Examination was normal. CPK was 65 IU/l.

MATERIALS AND METHODS

All biopsies were taken from vastus lateralis under local anæsthesia. Transverse and longitudinal 10 μm cryostat sections were stained by hæmatoxylin and eosin, Gomori's trichrome, and periodic acid-Schiff (PAS) techniques. Histochemically the biopsies were stained for succinic dehydrogenase, myophosphorylase, NADH-tetrazolium reductase, and ATP-ase pre-incubated at pHs of 9.4, 4.6 and 4.2 (Dubowitz and Brooke, 1973).

Histograms of fibre size were constructed by measuring the diameters of 200 fibres on NADH preparations. Atrophy and hypertrophy factors were calculated by the method of Brooke and Engel (1969) (*see* figs. 2, 3 and 4).

RESULTS

Case 1

First biopsy. Routine stains showed moderate variation in fibre diameter, increased number of centrally-placed nuclei, and occasional necrotic fibres containing macrophages (fig. 5). There was no evidence of fibre splitting, or regenerative fibres.

In the histochemical preparations, all fibres could be separated easily and consistently into type 1 and type 2 fibres. Type 1 fibres comprised 60 per cent of the total indicating significant type 1 predominance. A central core of absent or markedly decreased oxidative enzyme activity was present in 93 per cent of the

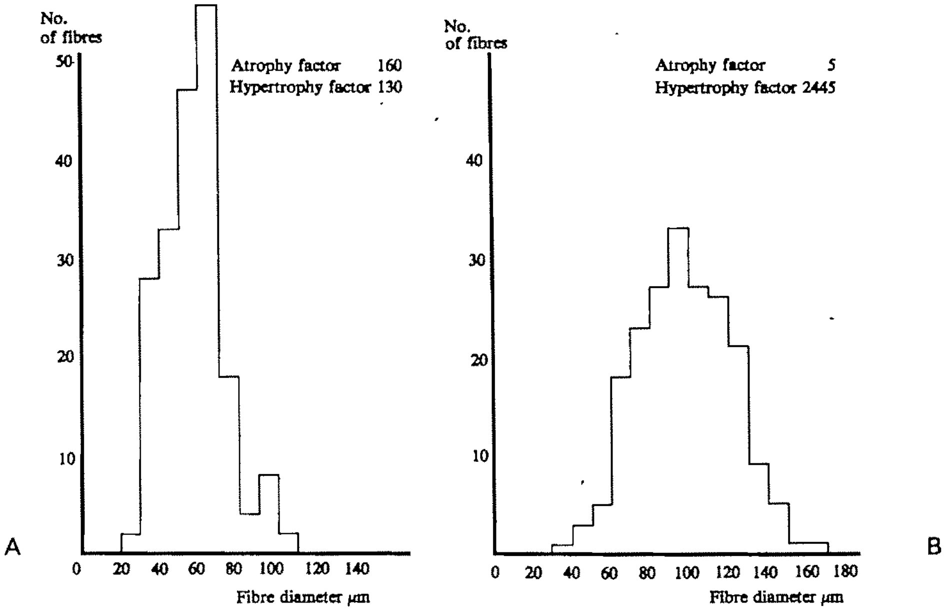

FIG. 2. Histograms of fibre size. *Case 1*, first biopsy. A, type 1 fibres; B, type 2 fibres.

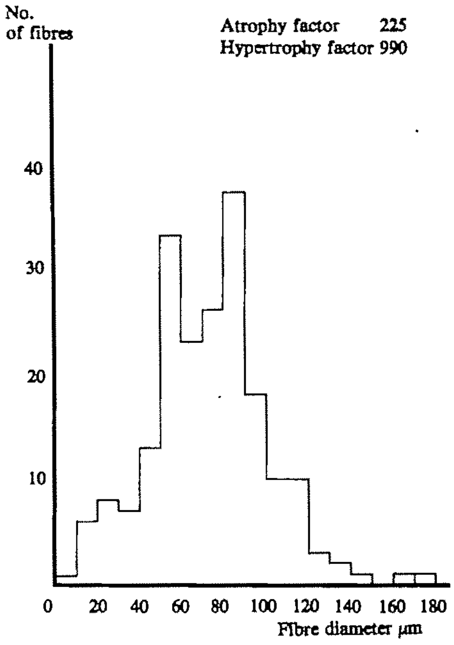

FIG. 3. Histogram of fibre size. *Case 1*, second biopsy. Type 1 fibres.

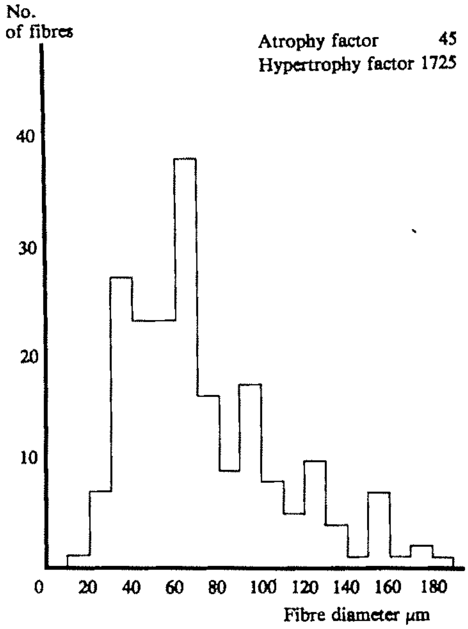

FIG. 4. Histogram of fibre size. *Case 2*, type 1 fibres.

type 1 fibres (fig. 6). Multiple cores were present in 20 per cent of the core-containing fibres. In longitudinal sections the cores extended for long distances along the length of the fibres. They were well seen in the Gomori's trichrome preparation, and with PAS they consisted of a central area of negative staining surrounded by a thin rim of dense positivity. Cores were not seen in type 2 fibres.

The atrophy factor for type 1 fibres was 160 (normal up to 150, Brooke and Engel, 1969) and the hypertrophy factor was normal. Type 2 fibres, although otherwise normal, showed marked hypertrophy, the hypertrophy factor being 2445 (normal up to 400).

Second biopsy. Routine stains showed essentially the same features as in the first biopsy—variation in fibre diameter, increased numbers of centrally-placed nuclei, and occasional necrotic fibres—but in addition fibre splitting was seen in occasional large fibres. Regenerative fibres were not seen.

Histochemically the type 1 fibre predominance (type 2 fibre paucity) was more marked, 96 per cent of the fibres staining as type 1 in the NADH preparations. Cores were present in 63 per cent of the type 1 fibres, being multiple in 18 per cent (fig. 7). Occasional fibres were seen, however, which stained positively with both NADH and ATPase at pH 9.4. The few remaining type 2 fibres appeared histochemically normal but tended to occur in groups rather than being scattered throughout the biopsy. For the type 1 fibres the atrophy factor was increased at 225, and the hypertrophy factor was also raised at 990.

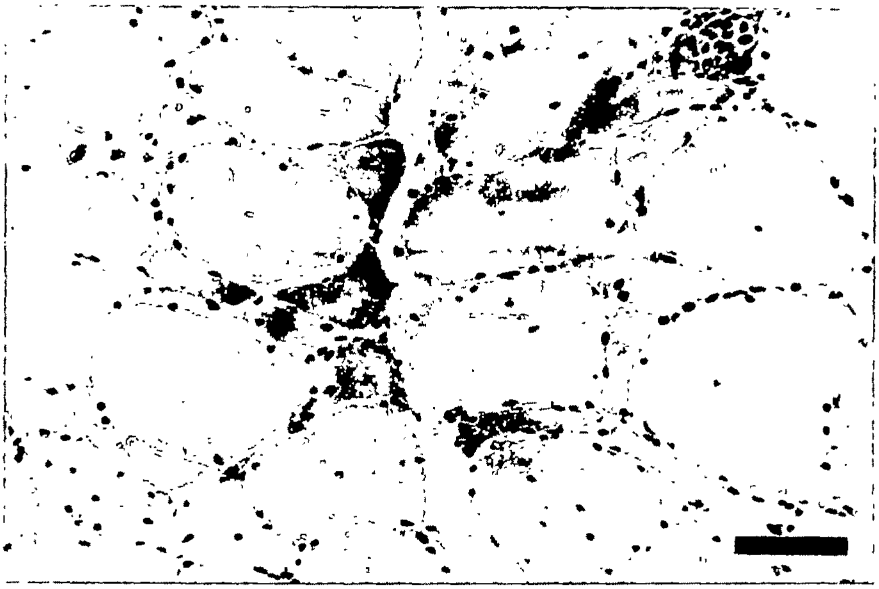

FIG. 5. *Case 1*, first biopsy, showing variation in muscle fibre diameter, multiple internally-placed nuclei, and a necrotic fibre undergoing phagocytosis (*top right*). Hæmatoxylin and Eosin. Bar = 100 μm

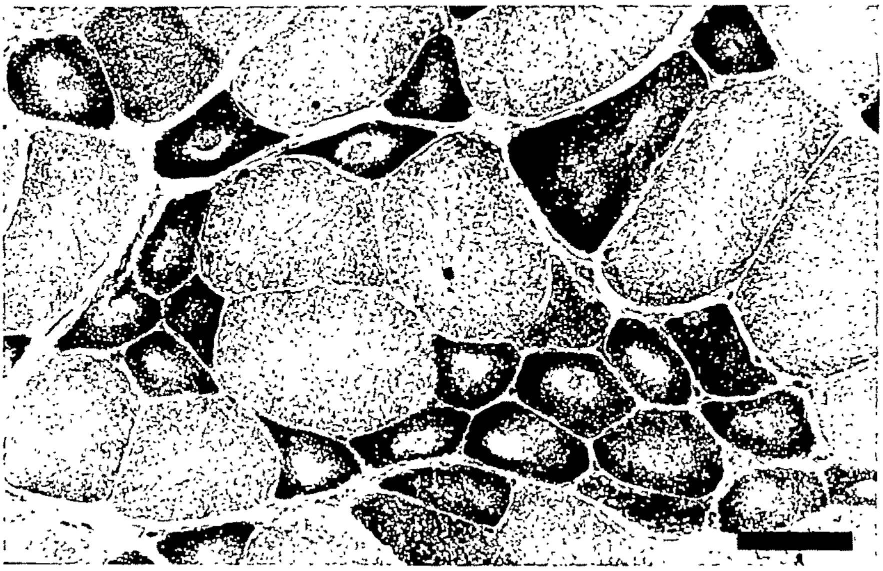

FIG. 6. *Case 1*, first biopsy NADH. Bar = 100 μm.

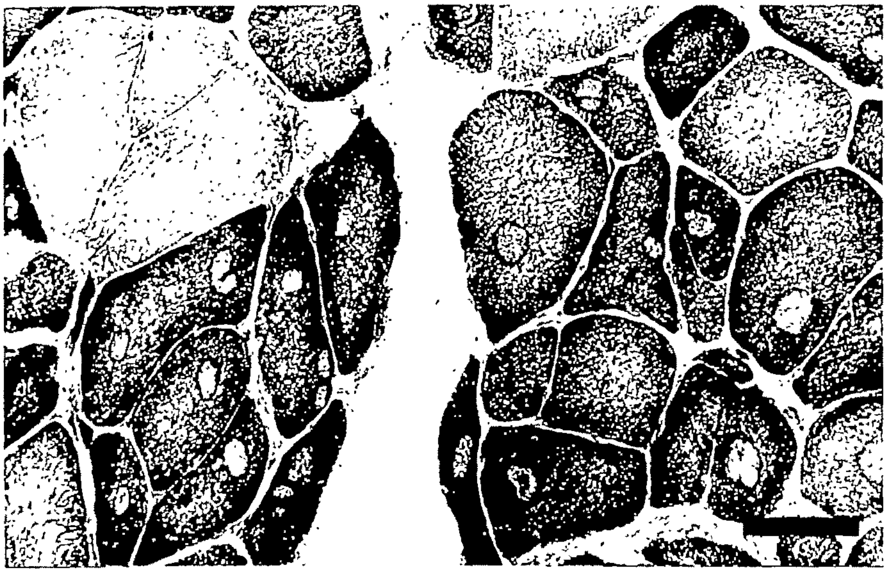

FIG. 7. *Case 1*, second biopsy NADH. Bar = 100 μm.

Case 2

Routine stains showed a marked variation in fibre diameter, some fibres up to 180 μm being seen. Centrally-placed nuclei occurred in only a few fibres (fig. 8). There was no evidence of fibre splitting, muscle fibre necrosis, phagocytosis or regeneration.

Histochemically less than 0.5 per cent of fibres stained as type 2 fibres, the remainder staining as type 1. The histochemical reaction of both fibre types was consistently reproducible, and no fibres stained with both NADH and ATPase at pH 9.4. Cores were present in 74 per cent of type 1 fibres; nearly all of them possessed a rim of increased positivity and there was a higher percentage of fibres containing multiple cores than in Case 1 (fig. 9). Occasional peripherally-situated cores were seen. In longitudinal sections the cores extended for long distances along the fibres, and PAS stains showed appearances similar to Case 1. The hypertrophy factor for the type 1 fibres was raised at 1725. The few type 2 fibres seen appeared normal and did not contain cores.

DISCUSSION

We have described 20 members of the H family from four generations, 6 of whom have clinical and biochemical evidence of myopathy. Of the remainder, 2 have elevated CPK levels without clinical muscle weakness, one has pes cavus and

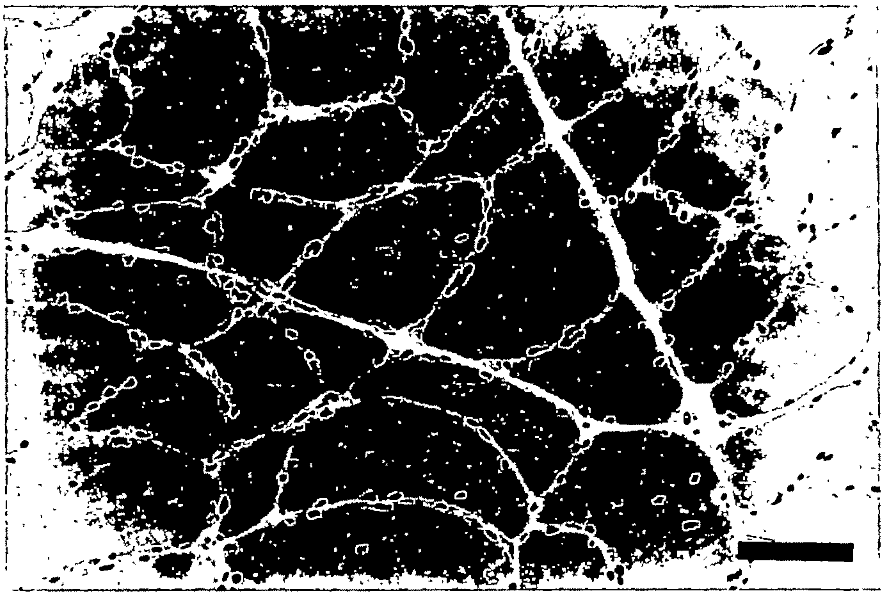

FIG. 8. *Case 2*, showing moderate variation in muscle fibre diameter with some fibres containing internally-placed nuclei. (Hæmatoxylin and Eosin). Bar = 100 μm.

scoliosis as his only abnormalities and 11 are normal. Muscle biopsy from Cases 1 and 2 showed central core disease.

In common with other families with central core disease the inheritance is dominant, the muscle weakness is proximal and there is an increased incidence of minor musculoskeletal abnormalities. This family differs from those described previously in that the cases with myopathy show two distinct clinical presentations.

Cases 2, 7, 8 and 10 have all had symptoms of weakness which can be dated back to an early age, and which have not progressed over the years. They therefore have a congenital non-progressive myopathy and are similar to the patients described by Shy and Magee (1956) in their original report. Cases 1 and 3, however, date their first symptoms of weakness to the ages of 49 and 66 years respectively, having had no evidence of motor disability in their early lives.

Case 1 is unusual, not only in the late onset of his symptoms, but also in the progression which these symptoms and signs have shown over eighteen months of follow-up. This clinical progression was accompanied by changes in the muscle histology which we think are relevant to the pathogenesis of central core disease. The first biopsy, taken twelve months after the start of his symptoms, showed reduced number of type 2 fibres which were abnormally large. Eighteen months later the appearances were quite different in that, while cores were still present in many type 1 fibres, type 2 fibres had almost completely disappeared and there were occasional fibres with staining characteristics of both type 1 and type 2 fibres.

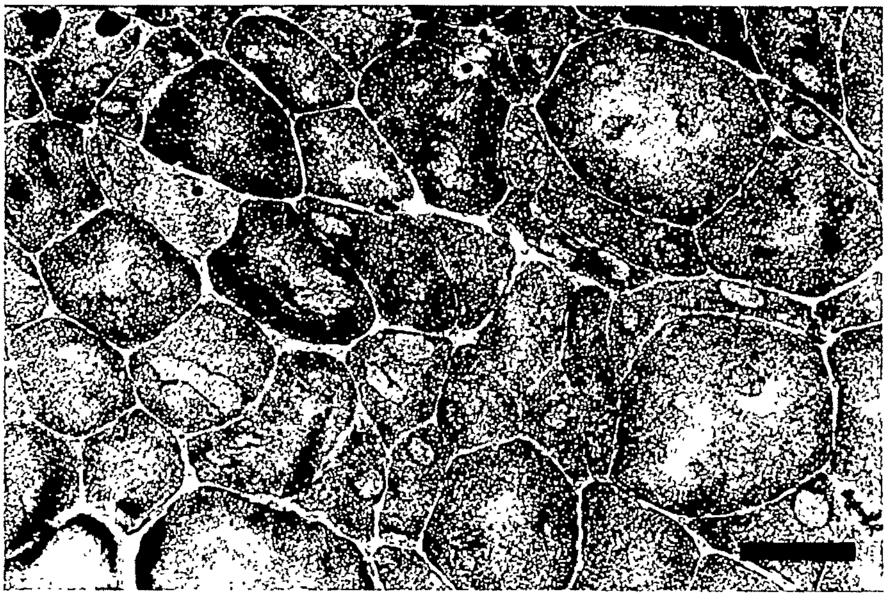

FIG. 9. *Case 2*, NADH. Bar = 100 μm.

These correspond to the type 3 fibre of Coërs, Telerman-Toppet, Gerard, Szliwowski, Bethlem and van Wijngaarden (1976), and are thought to represent fibres which are being reinnervated by an axon of another type.

Coërs, Telerman-Toppet, Gerard, Szliwowski, Bethlem and van Wijngaarden (1976) also reported hypertrophied type 2 fibres in two cases of central core disease, and Dubowitz (1967), in experiments using rabbits, noted hypertrophied fibres and central cores during reinnervation. The histological findings in the two biopsies of Case 1—'disappearing' type 2 fibres, type 2 fibre hypertrophy, type 3 fibres and central cores—would therefore be compatible with reinnervation of type 2 fibres by type 1 axons.

The biopsy in Case 2 showed even fewer type 2 fibres than the second biopsy of Case 1. Many type 1 fibres, in addition to containing cores, were abnormally large, but type 3 fibres were not seen. Presumably as the clinical condition had been stationary since early life the loss of type 2 fibres had long been complete at the time of biopsy.

The degree of weakness present in Cases 1 and 2 appears to vary with the amount of type 2 fibre loss. Thus Case 1 initially showed much less weakness than Case 2 but at the time of the second biopsy their disabilities were comparable. This relationship has been a feature of many of the previously recorded cases of central core disease. Complete or almost complete loss of type 2 fibres has always been associated with a congenital and non-progressive myopathy (Engel, Foster, Hughes, Huxley and Mahler, 1961; Armstrong, Koenigsberger, Mellinger and

Lovelace, 1971; Isaacs, Heffron and Badenhorst, 1975), whereas when type 2 fibres have been present in significant, although always reduced, numbers the clinical manifestations have been more varied and the muscle weakness less severe. These cases include a congenital myopathy associated with malignant hyperpyrexia (Denborough *et al.*, 1973), a woman with progressive pes cavus (Telerman-Toppet, Gerard and Coërs, 1973) and a 5-year-old boy with minimal symptoms (Dubowitz and Roy, 1970, Case 2). The family described by Morgan-Hughes, Brett, Lake and Tomé (1973) is of particular interest in this respect; the mother had had non-progressive weakness since early childhood and had a proximal myopathy. Muscle biopsy contained 97 per cent of type 1 fibres, of which 45 per cent had cores present. An asymptomatic 6-year-old daughter had minimal muscle weakness and her biopsy showed 83 per cent of type 1 fibres but no evidence of cores. A 3-year-old son with a congenital myopathy had 92 per cent type 1 fibres on muscle biopsy but again no cores. Morgan-Hughes *et al.* (1973) suggested that central cores did not represent the primary structural abnormality of this condition.

The elevated blood levels of CPK described in the present family have not been a feature of most reported cases of central core disease. Exceptions have included the patients reported by Denborough *et al.* (1973) and Eng, Epstein, Engel, McKay and McKay (1978) in whom central cores were found in association with malignant hyperpyrexia. This complication has not occurred in our family but the number of anæsthetic procedures has been small.

Raised CPK levels were also found in Cases 6 and 11 in the absence of symptoms or signs of muscle disease. It seems likely that they have a subclinical form of central core disease and may eventually develop a myopathy of late-onset. Both have declined further investigation at present.

The electrocardiographic abnormality seen in Case 2 merits comment in that the Wolff-Parkinson-White syndrome and other disturbances of cardiac rhythm have not been described in patients with central core disease. There had been no cardiac symptoms, and it is possible that the association here may be fortuitous.

In conclusion, our observations of the H family suggest that in central core disease there is reinnervation of type 2 fibres by type 1 axons. As type 2 fibres become reinnervated, symptoms of muscle weakness may appear, progressing until all type 2 fibres have been replaced, at which point progression ceases. The age of onset and rate of progression of this process will determine the clinical presentation; thus, if the process is complete at or around the time of birth a congenital and non-progressive myopathy will result. If the rate of progression is sufficiently slow then symptoms may not develop at all. Elucidation of the cause of this reinnervation process must wait until type 1 and type 2 motor neurons are as easily studied as their respective muscle fibres.

SUMMARY

A family is described whose members showed different clinical presentations of central core disease. In 4 members the myopathy was congenital and non-progressive, but in 2, muscle weakness first developed in adult life. Two further members had raised CPK levels without muscle weakness.

Muscle weakness in one of the late-onset cases increased over eighteen months. This was associated with evidence of loss of type 2 fibres and the appearance of type 3 fibres on muscle biopsy. It is suggested that central core disease involves reinnervation of type 2 fibres by type 1 axons, and that the clinical manifestation of the disease depends on the age of onset and rate of progression of this process.

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REFERENCES

ARMSTRONG, R. M., KOENIGSBERGER, R., MELLINGER, J. and LOVELACE, R. E. (1971) Central core disease with congenital hip dislocation: study of two families. *Neurology, Minneapolis*, **21,** 369–376.

BETHLEM, J., VAN GOOL, J., HÜLSMANN, W. C. and MEIJER, A. E. F. H. (1966) Familial non-progressive myopathy with muscle cramps after exercise. *Brain*, **89,** 569–588.

BROOKE, M. H. and ENGEL, W. K. (1969) The histographic analysis of human muscle biopsies with regard to fibre types. Diseases of the upper and lower motor neuron. *Neurology, Minneapolis*, **19,** 378–393.

COËRS, C., TELERMAN-TOPPET, N., GERARD, J. M., SZLIWOWSKI, H., BETHLEM, J. and VAN WIJNGAARDEN, G. K. (1976) Changes in motor innervation and histochemical pattern of muscle fibres in some congenital myopathies. *Neurology, Minneapolis*, **26,** 1046–1053.

DENBOROUGH, M. A., DENNETT, X. and ANDERSON, R. McD. (1973) Central core disease and malignant hyperpyrexia. *British Medical Journal*, **i,** 272–273.

DUBOWITZ, V. (1967) Pathology of experimentally re-innervated skeletal muscle. *Journal of Neurology, Neurosurgery and Psychiatry*, **30,** 99–110.

—— and BROOKE, M. H. (1973) *Muscle Biopsy: a Modern Approach.* London: W. B. Saunders, Chapter 2, pp. 20–33.

—— and PLATTS, M. (1965) Central core disease of muscle with focal wasting. *Journal of Neurology, Neurosurgery and Psychiatry*, **28,** 432–437.

—— and ROY, S. (1970) Central core disease of muscle: clinical, histochemical and electron microscopic studies of an affected mother and child. *Brain*, **93,** 133–146.

ENG, G. D., EPSTEIN, B. S., ENGEL, W. K., McKAY, D. W. and McKAY, R. (1978) Malignant hyperthermia and central core disease in a child with congenital dislocating hips. *Archives of Neurology, Chicago*, **35,** 189–197.

ENGEL, W. K., FOSTER, J. B., HUGHES, B. P., HUXLEY, H. E. and MAHLER, R. (1961) Central core disease—an investigation of a rare muscle cell abnormality. *Brain*, **84**, 167–185.

ISAACS, H., HEFFRON, J. J. A. and BADENHORST, M. (1975) Central core disease—a correlated genetic, histochemical, ultramicroscopic and biochemical study. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 1177–1186.

MORGAN-HUGHES, J. A., BRETT, E. M., LAKE, B. D. and TOMÉ, F. M. S. (1973) Central core disease or not? Observations on a family with a non-progressive myopathy. *Brain*, **96**, 527–536.

SHAFIQ, S. A., GORYCKI, M. A., ASIEDU, S. A. and MILHORAT, A. T. (1969) Tenotomy. Effects on the fine structure of the soleus of the rat. *Archives of Neurology, Chicago*, **20**, 625–633.

SHY, G. M. and MAGEE, K. R. (1956) A new congenital non-progressive myopathy. *Brain*, **79**, 610–621.

TELERMAN-TOPPET, N., GERARD, J. M. and COËRS, C. (1973) Central core disease. A study of clinically unaffected muscle. *Journal of the Neurological Sciences*, **19**, 207–223.

(*Received January 9, 1979*)

Brain (1979), **102**, 595–608

EFFECTS OF BRAIN-STEM AND THALAMIC LESIONS ON THE CORNEAL REFLEX

AN ELECTROPHYSIOLOGICAL AND ANATOMICAL STUDY

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THE corneal reflex is the response to the application of a light mechanical stimulus to the surface of the cornea. The reflex response is a bilateral closure of the eyelids following contraction of the orbicularis oculi muscles. From a receptive network of free nerve endings within the cornea afferent impulses of the corneal reflex are conducted along unmyelinated and small myelinated fibres in the long ciliary branch of the ophthalmic division of the trigeminal nerve to the pons (Windle, 1926; Tower, 1940; Lele and Weddell, 1959). From the pons they descend into the medulla oblongata along fibres of the spinal trigeminal tract and terminate upon cells of the ipsilateral spinal nucleus of the fifth cranial nerve (Windle, 1926; Sjöquist, 1938; Rowbotham, 1939; Smyth, 1939; Moffie, 1971).

The exact pathways which lead from this nucleus to the ipsilateral and contralateral facial nuclei are not known. It is a common clinical experience that the corneal reflex is diminished or absent in lesions of the contralateral parietal lobe (Oliver, 1952; Ross, 1972). On the basis of this observation Oliver (1952) has suggested that the reflex may occur along a long-loop pathway reaching the contralateral cerebral cortex by way of fibres of the trigeminothalamic tract. This tract is incorporated in the medial lemniscus, and in the rostral half of the pons it comes into close relationship with fibres of the spinothalamic tract. The anatomical basis of such a long-loop reflex remains unclear. Other authors (Kugelberg, 1952; Magladery and Teasdall, 1961; Rushworth, 1962) have concluded from electrophysiological studies that connections from the spinal fifth complex to the facial nuclei are relayed through multiple intramedullary synaptic connections whose location has not been defined. The reflex is regarded as nociceptive.

The purpose of this study was to investigate the corneal reflex in patients with medullary, midbrain and thalamic lesions in an attempt to define the trigeminofacial pathway which subserves this reflex. Clinical observations of the corneal reflex evoked by light touch of the cornea with a wisp of cotton wool are compared with physiological results using an electromyographic technique.

METHODS

The technique used to record the corneal reflex has been described previously (Ongerboer de Visser, Mechelse and Megens, 1977). The reflex was evoked by touching the cornea with a 2 mm diameter metal sphere which was connected to an electronic trigger circuit. As soon as contact between subject and sphere was established, this touch-sensitive circuit delivered a pulse which triggered the sweep of a persistence oscilloscope.

Reflex responses were recorded from the orbicularis oculi muscles by surface electrodes placed over the lower eyelids. A stimulus to either cornea normally elicits a direct (ipsilateral) and a consensual (contralateral) reflex response. The latency time was measured from the start of the oscilloscope sweep to the initial deflection of the evoked muscle potential. The latency of the corneal reflex responses range widely from 36 to 64 ms in normal subjects. In other words, because of the wide range of corneal reflex latencies, comparison of the reflex latency on one side with the latency on the other side gives a more reliable indication of the presence of a lesion in the reflex pathway. Conduction in the ipsilateral and contralateral reflex pathways from either eye can be tested and compared by measuring the latency times of four possible responses: in any individual normal subject, (1) when either cornea is touched the latency of the contralateral response does not exceed the latency of the ipsilateral response by more than 8 ms; (2) the latency of the ipsilateral response evoked from either cornea does not differ by more than 10 ms from the latency of the ipsilateral response evoked from the other cornea; (3) the latency of the contralateral response evoked from either cornea does not differ by more than 10 ms from the latency of the contralateral response evoked from the other cornea.

In the present study corneal reflexes were recorded in 9 patients with a lateral medullary syndrome (Wallenberg), in one patient with a midbrain lesion and in 2 patients with a thalamic lesion. All patients were in an alert state during the recording.

The 9 patients showing clinical signs and symptoms of Wallenberg's syndrome (Currier, Giles and

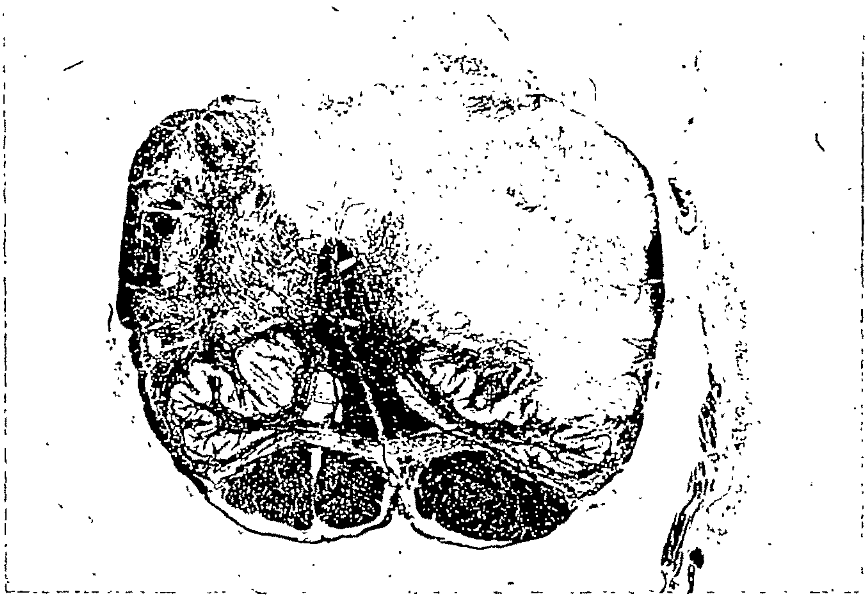

FIG. 1. Cross section through the lower part of the medulla oblongata showing a lateral infarction in one of the type D cases. Note that the infarction involves, among other structures, the spinal fifth complex, its tract, and both the medial and lateral reticular formations. Klüver ×4.

De Jong, 1961; Fisher, Karnes and Kubik, 1961; Currier, 1969) ranged in age from 46 to 74 years. Five of these were also included in an earlier study concerning late blink reflex changes in Wallenberg's syndrome (Ongerboer de Visser and Kuypers, 1978). The 9 patients were divided into 3 groups according to the severity of the clinical signs and symptoms.

Group 1 consisted of 3 patients showing the typical syndrome and having the most severe degree of vertigo, imbalance, nausea, vomiting, dysphonia, dysphagia and hiccups. Autopsy was performed on 2 of them. In the first of these two patients a unilateral infarction in the lateral part of the medulla oblongata on the right side (fig. 1) extended from the level of the pontomedullary junction to the lower part of the inferior olive. The infarction included the descending spinal trigeminal tract and its nucleus, the vestibular complex, the lateral spinothalamic and ventral spinocerebellar tracts, and both the bulbar lateral and medial reticular formations. In the second patient the infarction involved mainly the spinal fifth nerve complex and its tract, and the lateral reticular formation, whereas the medial reticular formation was largely unaffected. A detailed description of this lesion has already been published (Ongerboer de Visser and Kuypers, 1978).

Group 2 consisted of 4 patients. Symptoms were less severe than in Group 1. Autopsy in one of these patients confirmed the clinical diagnosis: an infarction was found in the dorsolateral region of the medulla oblongata.

Group 3 consisted of 2 patients, in whom vertigo, nausea and vomiting lasted only one day. Pain sensation was slightly diminished in the ipsilateral half of the face and the contralateral side of the trunk. Cerebellar signs were minimal, but Horner's syndrome was present in both patients.

All 9 patients were examined electrophysiologically within the first week of their illness.

The patient with a midbrain lesion, who was 76 years old, showed a vertical-gaze paralysis, a nuclear ophthalmoplegia on the right side and a hemianalgesia on the left side. At autopsy a metastasis from a renal carcinoma was found in the lamina quadrigemina and the right side of the tegmentum, comprising the spinothalamic tract and the medial leminiscus. The left side of the tegmentum as well as the cerebral peduncles were spared (fig. 2).

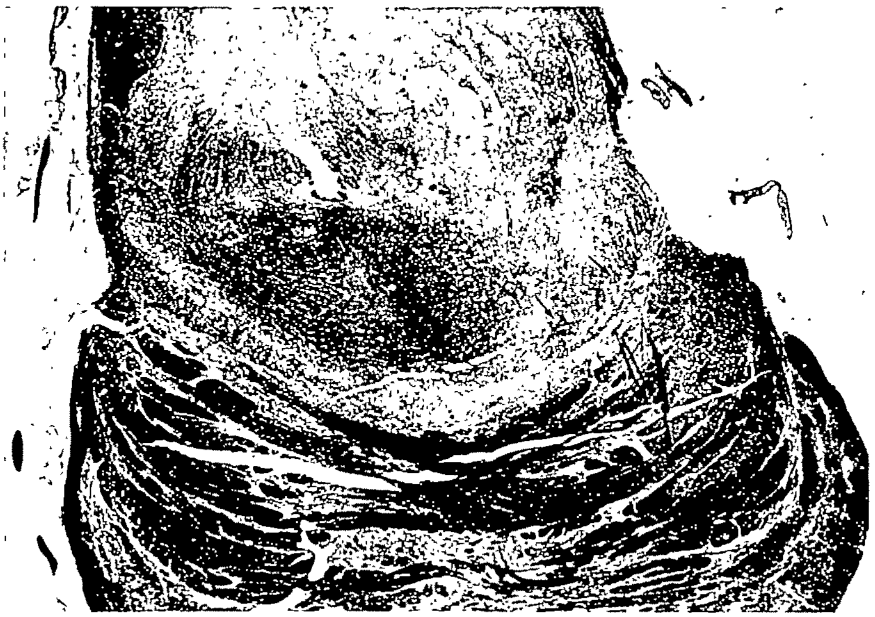

FIG. 2. Cross section through the mesencephalon showing the metastatic lesion on the right involving, besides other structures, also the spinothalamic tract and the medial lemniscus (arrows). Klüver ×4.

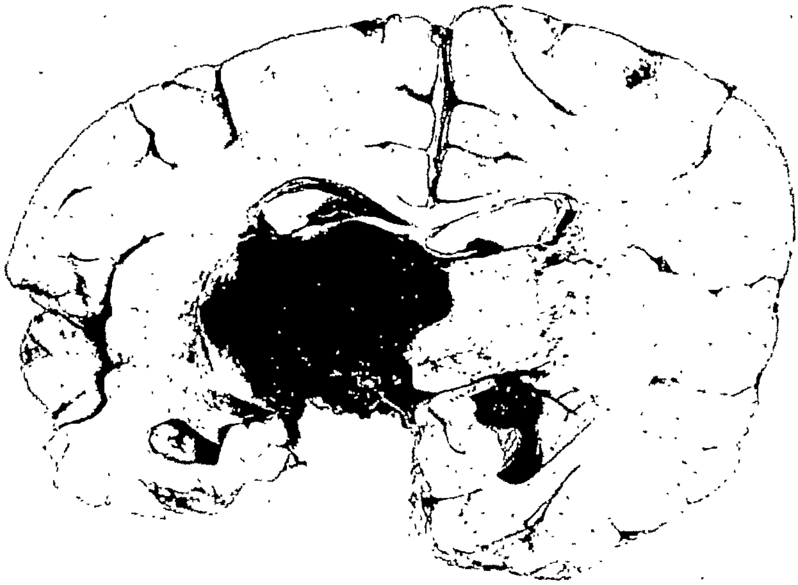

FIG. 3. Hæmorrhage in a hæmangioma of the left thalamus.

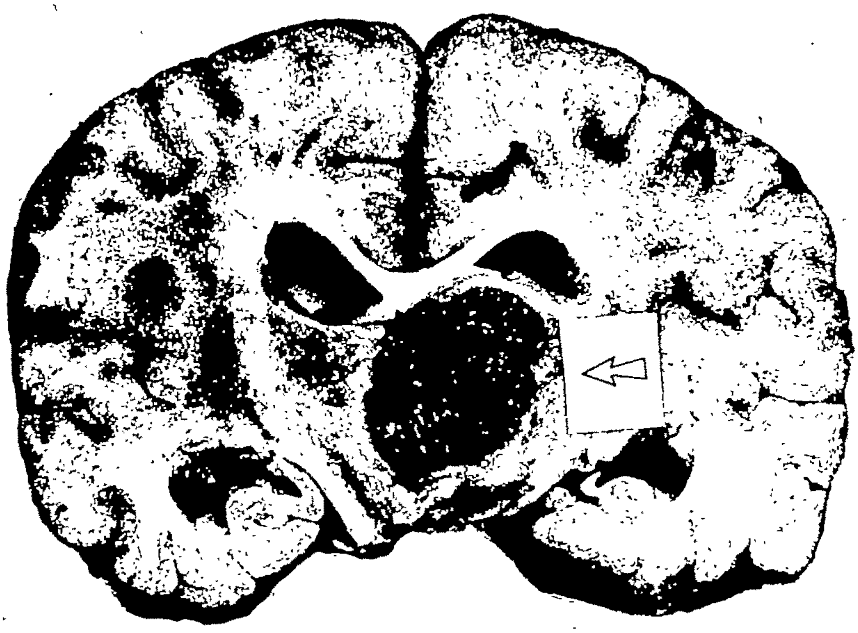

FIG. 4. Metastatic tumour in the right thalamus (arrowed).

In 2 patients with thalamic lesions, 36 and 52 years old, pain sensation was diminished in the contralateral half of the face and the trunk, postural sense was impaired and a slight ataxia was present on the opposite side of the body. Autopsy was performed on both of them. In the first patient a hæmangioma was found in the left thalamus (fig. 3) and the second had a metastatic tumour from a bronchial adenocarcinoma in the right thalamus (fig. 4).

RESULTS

All the patients with Wallenberg's syndrome showed abnormal corneal reflexes, both clinically and electrophysiologically. Clinical examination was done first by the clinician. The abnormal findings observed with the electrophysiological method could be divided into four different types.

The first type of abnormality (type A, fig. 5) was present in 3 cases. In 2 cases the abnormality consisted of a bilateral delay (12 and 20 ms when compared with the normal side) of the reflex responses upon right-sided stimulation when the lesion was on the right side. In the third case, there was a bilateral delay (24 ms) of the reflex responses upon left-sided stimulation when the lesion was on the left. The

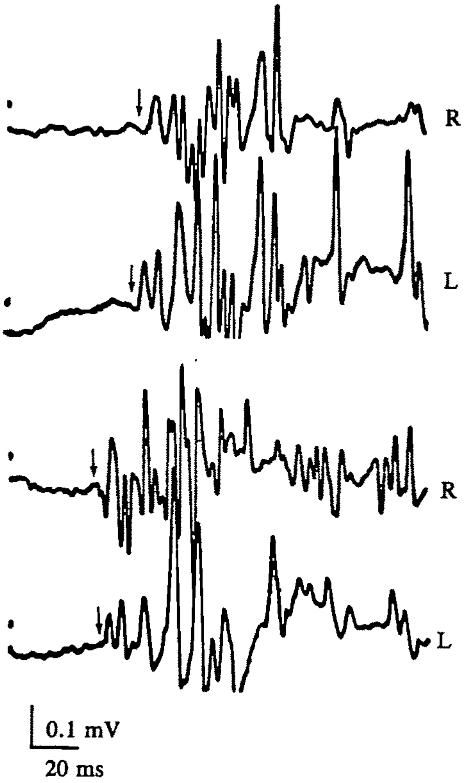

FIG. 5. Example of type A abnormality of the corneal reflex in lateral medullary lesions. In this case the lesion is on the right side. *Upper* pair of traces: bilateral delay (20 ms) of the corneal reflex after stimulation of the right cornea. *Lower* pair of traces: normal corneal reflex after stimulation of the left cornea. R = right; L = left; in this and subsequent figures.

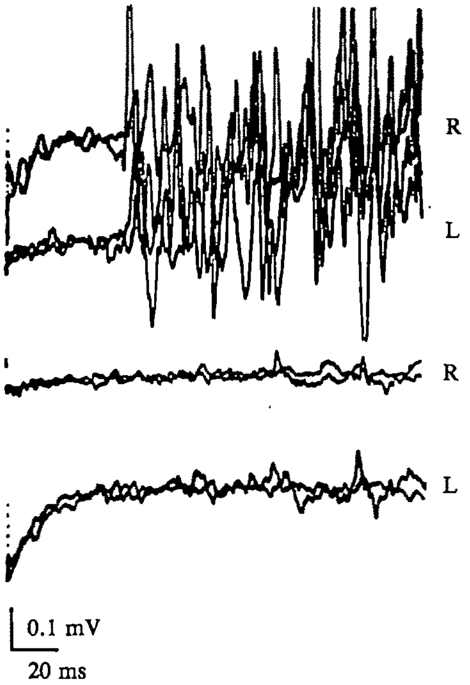

FIG. 6. Example of type B abnormality of the corneal reflex in lateral medullary lesions. In this case the lesion is on the left. *Upper* pair of traces: normal corneal reflex after stimulation of the right cornea. *Lower* pair of traces: bilateral absence of the corneal reflex after stimulation of the left cornea ipsilateral to the lesion. Two responses are superposed.

reflex responses were normal bilaterally when the normal side was stimulated. Two of these 3 cases belonged to patient Group 3 and one case to Group 2.

The second type of abnormality (type B, fig. 6), present in 2 cases, consisted of a bilateral absence of the reflexes when the cornea on the side of the lesion was stimulated. The reflex responses were normal bilaterally when the stimulus was applied to the cornea on the normal side. These 2 cases belonged to Group 2.

The third type of abnormality (type C, fig. 7) was seen in one case. When the cornea on the side of the lesion was stimulated both the direct and the consensual reflex responses were consistently absent. However, when the cornea on the unaffected side was stimulated a normal reflex response was seen on that side, whereas the contralateral reflex response on the side of the lesion showed a latency time which was markedly longer (20 ms) than the latency of the normal reflex response. This patient belonged to Group 1 with the most severe symptoms.

The fourth type of abnormality (type D, fig. 8) was observed in 3 cases. This type consisted of a bilateral absence of reflex responses upon stimulation of the cornea on the side of the lesion as in type B and C abnormality. However, a stimulus to the cornea on the normal side only elicited a reflex response on that side, but no response on the contralateral (affected) side. Two of these patients belonged to

Group 1 and subsequently died. The remaining case belonged to Group 2. The lateral infarction in the medulla oblongata in one patient is shown in fig. 1. The medullary infarction in the other patient has been described earlier in detail (Ongerboer de Visser and Kuypers, 1978).

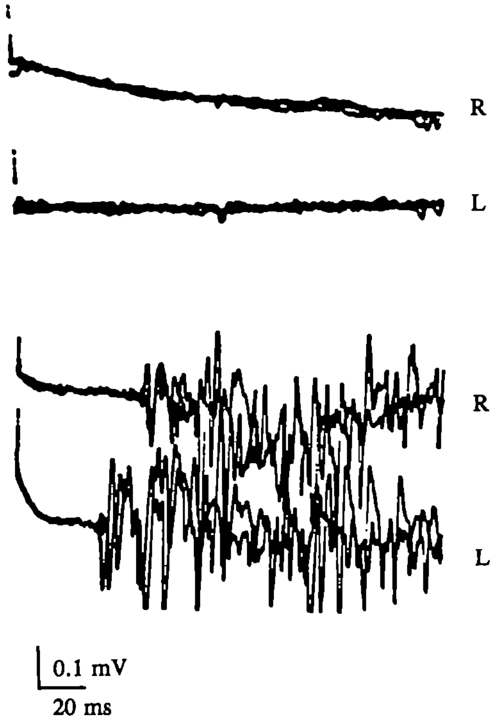

FIG. 7. Example of type C abnormality of the corneal reflex in lateral medullary lesions. The lesion is on the right side. *Upper* pair of traces: bilateral absence of the corneal reflex after stimulation of the right cornea. *Lower* pair of traces: normal corneal reflex response on the left (the intact side) and a delay (20 ms) of the reflex response on the right (the side of the lesion) after stimulation of the left cornea. Two responses are superposed.

Comparison of the results obtained with electrophysiological and clinical examination of the corneal reflex in the nine patients with Wallenberg's syndrome led to the following conclusions. First, the bilateral delayed reflex responses upon stimulation to the affected side in type A abnormality correlated well with a bilaterally diminished corneal reflex found on clinical examination. Second, for the electrophysiological type B abnormality (bilateral absence of reflex responses on stimulation of the affected side) routine clinical examination confirmed this abnormality in one case; in the other case the corneal reflex was diminished bilaterally when tested clinically. Third, there was no correlation between the electrophysiological types C and D abnormalities and the clinical observations. The delayed reflex response contralateral to the normal side (fig. 7) found in type C abnormality was, of course, not seen in the clinical examination; both the

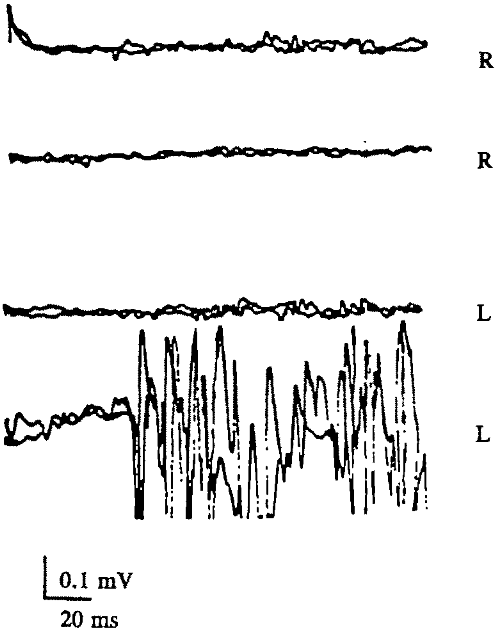

FIG. 8. Example of type D abnormality of the corneal reflex in lateral medullary lesions. The lesion is on the right side. *Upper* pair of traces: bilateral absence of the corneal reflex after stimulation of the right cornea. *Lower* pair of traces: normal corneal reflex response on the left (the intact side) and absence of reflex response on the right (the side of the lesion) after stimulation of the right cornea. The lateral infarction in this case is shown in fig. 1.

contralateral and the ipsilateral reflex response were clinically normal. The absent reflex response contralateral to the normal side (fig. 8) found in type D abnormality was also not observed clinically; the reflex was indicated to be normal bilaterally, although special attention was not given to reflex responses in the contralateral eyelids.

The patients with the midbrain lesion (fig. 2) and the two patients with the thalamic lesions (figs. 3 and 4) showed normal results both electrophysiologically and clinically.

DISCUSSION

Changes in the corneal reflex play an important role in the clinical diagnosis of lesions of the trigeminal nerve and its connections in brain-stem disease. Recording brain-stem reflexes by electrophysiological means makes it possible to detect abnormalities that may not be found on clinical examination (Kimura, 1973; Ongerboer de Visser and Goor, 1974, 1976*a*, *b*; Goor and Ongerboer de Visser, 1976; Ongerboer de Visser *et al.*, 1977; Ongerboer de Visser and Kuypers, 1978). Correlation of abnormal findings with post-mortem results may help to determine the pathways of these reflexes within and above the brain-stem.

In the patients with Wallenberg's syndrome comparison between the results found on clinical and electrophysiological examination demonstrated that the clinically diminished corneal reflex correlated well with the observed delayed electrophysiological corneal reflex responses (type A abnormality, fig. 5). The electrophysiologically absent corneal reflex responses in type B abnormality (fig. 6) were clinically diminished in one patient and absent in the other. The abnormal reflex responses on the affected side in the electrophysiological type C and D abnormalities (figs. 7 and 8, respectively) upon stimulation on the normal side were not observed on clinical examination where the reflex was regarded to be normal bilaterally. These comparisons illustrate that electrophysiological recording of the corneal reflex can reveal clinically undetectable abnormalities.

Anatomical investigations in two cases with type D abnormality which belonged to Group 1 with the most severe symptoms, showed rather extensive lesions; a photograph of one of the lesions is shown in fig. 1 and the other lesion was described in a previous study (Ongerboer de Visser and Kuypers, 1978). These findings suggest that when type D abnormality occurs in Wallenberg's syndrome the lesion can be expected to extend deeply into the lateral medullary region.

The present electrophysiological findings help to determine the arrangement of the fibre connections underlying the bilateral response of the corneal reflex. In the cases with type A and B abnormalities a normal bilateral reflex response could still be evoked upon stimulation of the cornea on the normal side. This leads to the conclusion that the pathway by which the bilateral corneal reflex response is transmitted involves the ipsilateral spinal trigeminal tract and the area of the ipsilateral spinal trigeminal nucleus (fig. 9). In the cases with type C and D abnormality the bilateral reflex response was absent upon stimulation of the cornea on the affected side as in the cases with type B abnormality. However, when the cornea on the intact side was stimulated a normal reflex response was only observed on the intact side and either a delayed response in type C abnormality or no response in type D abnormality occurred on the affected side. This leads to two further conclusions. First, the corneal reflex response on the stimulated side is conducted along an ipsilateral ascending medullary route which passes from the caudal area of the spinal fifth complex to the ipsilateral facial nucleus (fig. 9). Secondly, because of either the delay or the absence of the reflex response on the affected side upon stimulation of the cornea on the intact side, the contralateral corneal reflex response must be established by way of an ascending medullary pathway, which crosses the midline in the caudal medulla oblongata before ascending to the contralateral facial nucleus (fig. 9). In one patient with type D abnormality an anatomical lesion was found which included both the bulbar lateral and medial reticular formations (fig. 1). In the other patient with type D abnormality the lesion involved the lateral reticular formation and largely spared the medial reticular formation (Ongerboer de Visser and Kuypers, 1978). These facts suggest that the ipsilateral and the contralateral ascending medullary pathway to the facial nuclei are located in the lateral reticular formation of the lower brain-stem.

With respect to the above-mentioned conclusions it is of interest to note that according to Holstege and Kuypers (1977) and Holstege, Kuypers and Dekker (1977), the bulbar lateral reticular formation in the cat contains a lateral and a medial propriobulbar fibre system; the former distributes fibres to the bulbar motor nuclei mainly homolaterally, whereas the latter tends to distribute fibres to these nuclei bilaterally. The medial propriobulbar system also contains fibres arising from neurons at the level of the obex and passing to the intermediate facial subnucleus on both sides. This subnucleus is thought to innervate the orbicularis oculi muscle (Courville, 1966). If these connections found in the cat also exist in man, they would explain the type C and D abnormality, because a unilateral trigemino-reticular lesion would not only block the ipsilateral trigeminal projection to the caudal medullary neurons on the affected side which, in turn, project to

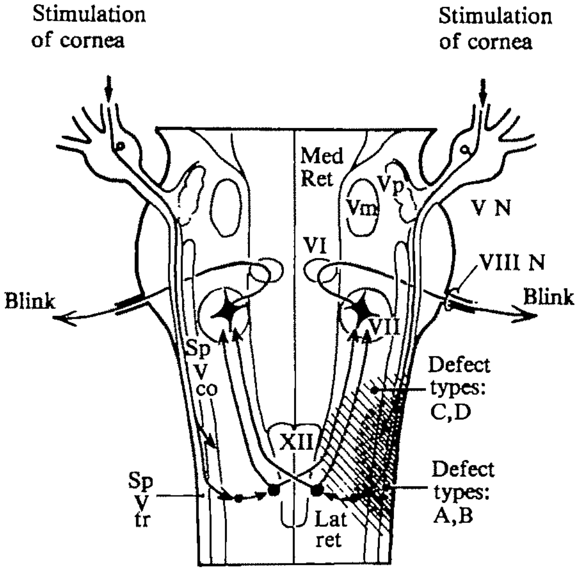

FIG. 9. Diagram showing the presumed location of the bulbar interneurons subserving the two responses of the corneal reflex. A lesion involving the double-shaded area on the right would only interfere with the bilateral response elicited by stimulation of the cornea on the affected side. A larger lesion also involving the lightly shaded area would also interfere with the bilateral response on the affected side elicited by stimulation of the cornea on the intact (left) side.

VN = trigeminal nerve.
Vm = trigeminal motor nucleus.
Vp = trigeminal principal sensory nucleus.
Sp V tr = spinal trigeminal tract.
Sp V co = spinal trigeminal complex.
VI = abducens nucleus.
VII = facial nucleus.
VIII N = facial nerve.
XII = hypoglossal nucleus.
Med. ret. = medial reticular formation.
Lat. ret. = lateral reticular formation.

motoneurons of the orbicularis oculi muscle on both sides, but would also interfere with the crossed ascending fibres which are distributed from the corresponding neurons on the intact side to the motoneurons of the orbicularis oculi muscle on the affected side.

The corneal reflex may be clinically diminished or absent in patients with deep lesions of the contralateral parietal lobe (Oliver, 1952; Ross, 1972) and so it is remarkable that this reflex was normal in our patients with lesions of the midbrain and the thalamus. These lesions involved on one side the secondary sensory fibres, which ascend from the spinal nucleus of the fifth nerve in association with the medial lemniscus to the posterior ventromedial nucleus of the thalamus. From our findings it may be concluded that for the corneal reflex possible impulses from the bulbar reflex system to the parietal lobe are not conducted through the contralateral thalamus alone. From experimental work (Brodal and Walberg, 1960; Kuypers, 1960; Jones and Wise, 1977; Brodal, 1978) it has become clear that there is an extensive projection of the sensorimotor cortex upon brain-stem nuclei and that the spinal trigeminal complex receives fibres from the postcentral cortex (Kuypers, 1960). In our cases with midbrain and thalamic lesions the pyramidal tracts were not involved, so that an excitatory influence of the parietal lobe on the corneal reflex was not interrupted by these lesions.

Ongerboer de Visser and Kuypers (1978) proposed on the basis of results obtained in patients with Wallenberg's syndrome that the late component of the blink reflex and the corneal reflex utilize similar trigeminofacial connections passing through the lateral medulla oblongata. However, there are important differences between these reflexes. The corneal reflex showed a high degree of constancy of the intra-individual latency times and no facilitation or habituation, which is in contrast to the late blink reflex, showing clearly these phenomena (Magladery and Teasdall, 1961; Ongerboer de Visser *et al.*, 1977). Further, afferent impulses for the late blink reflex pass to a large extent along myelinated fibres of all diameters and to a lesser extent along small unmyelinated fibres of the supraorbital nerve (Windle, 1926). Afferent fibres in the ciliary nerves from the cornea, on the other hand, are for the most part small in diameter and slow in conduction (Tower, 1940; Lele and Weddell, 1959). They comprise a small fibre bundle and a narrow fibre spectrum in comparison with afferent fibres of the late blink reflex. Because of these differences it may be expected that lateral medullary lesions will affect the corneal reflex more often than the late component of the blink reflex.

SUMMARY

In 9 patients with Wallenberg's lateral medullary syndrome, one patient with a midbrain lesion involving the right side of the tegmentum, and 2 patients with a thalamic lesion, corneal reflexes were investigated by a new electromyographic technique. The electrophysiological results were compared with the results

obtained by clinical observation. In the lateral medullary lesions the electrophysiologically obtained reflex responses showed four types of abnormality. Type A consisted of a bilateral delay and type B a bilateral absence of the corneal reflex response to stimulation on the affected side in combination with a normal reflex response on both sides when the cornea on the normal side was stimulated. Type C, which was present in one case, and type D which was seen in 3 cases, consisted of a bilateral absence of the corneal reflex upon stimulation on the affected side; stimulation on the unaffected side produced a normal reflex response on the intact side in combination with, respectively, a delay or absence of the corneal reflex response on the affected side. Comparison of the clinical observations with the electrophysiological findings revealed minor discrepancies in type A and B abnormalities. However, the electrophysiological type C and D abnormalities were not detected by clinical observation. These findings demonstrate that electrophysiological recording of the corneal reflex may reveal clinically undetectable abnormalities.

From the electrophysiological findings it is concluded that the corneal reflex is conducted along medullary pathways running both ipsilaterally and contralaterally from the stimulated side before connecting, respectively, with the ipsilateral and contralateral facial nucleus. From the anatomical findings it is suggested that the ascending pathways from the spinal fifth nerve complex to the facial nuclei are located in the lateral reticular formation of the lower brain-stem.

The normal corneal reflex responses in the presence of thalamic and midbrain lesions involving nociceptive fibres in the trigeminothalamic tract do not support a previously postulated long-loop reflex arc passing through this tract. The suprabulbar influence upon the corneal reflex is discussed.

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REFERENCES

BRODAL, P. (1978) The cortico-pontine projections in the rhesus monkey. Origin and principles of organization. *Brain*, **101**, 251-284.

—— and WALBERG, F. (1960) Anatomical studies of some corticofugal connexions to the brain-stem. In: *Structure and Function of the Cerebral Cortex*. Proceedings of the Second International Meeting of Neurobiologists, Amsterdam, 1959. Edited by P. B. Tower and J. P. Schadé. Amsterdam: Elsevier.

COURVILLE, J. (1966) The nucleus of the facial nerve: the relation between cellular groups and peripheral branches of the nerve. *Brain Research, Amsterdam*, **1**, 338–354.

CURRIER, R. D. (1969) Syndromes of the medulla oblongata. In: *Handbook of Clinical Neurology*. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland Publishing Company. Vol. 2, pp. 217–237.

—— GILES, C. L. and DE JONG, R. N. (1961) Some comments on Wallenberg's lateral medullary syndrome. *Neurology, Minneapolis*, **2**, 778–791.

FISHER, C. M., KARNES, W. E. and KUBIK, C. S. (1961) Lateral medullary infarction—the pattern of vascular occlusion. *Journal of Neuropathology and Experimental Neurology*, **20**, 323–379.

GOOR, C. and ONGERBOER DE VISSER, B. W. (1976) Jaw and blink reflexes in trigeminal nerve lesions: an electrodiagnostic study. *Neurology, Minneapolis*, **26**, 95–97.

HOLSTEGE, G. and KUYPERS, H. G. J. M. (1977) Propriobulbar fibre connections to trigeminal, facial and hypoglossal motor nuclei. I. An antergrade degeneration study in cat. *Brain*, **100**, 239–264.

—— —— and DEKKER, J. J. (1977) The organization of the bulbar connections to the trigeminal, facial and hypoglossal motor nuclei. II. An autoradiographic tracing study in cat. *Brain*, **100**, 265–286.

JONES, E. G. and WISE, S. P. (1977) Size, laminal and columnar distribution of efferent cells in the sensorimotor cortex of monkeys. *Journal of Comparative Neurology*, **175**, 391–438.

KIMURA, J. (1973) The blink reflex as a test for brain-stem and higher central nervous system function. In: *New Developments in Electromyography and Clinical Neurophysiology*. Edited by J. E. Desmedt. Basel: Karger, Vol. 3, pp. 682–691.

KUGELBERG, E. (1952) Facial reflexes. *Brain*, **75**, 385–396.

KUYPERS, H. G. J. M. (1960) Central cortical projections to motor and somatosensory cell-groups. An experimental study in the rhesus monkey. *Brain*, **83**, 161–184.

LELE, P. P. and WEDDELL, G. (1959) Sensory nerves of the cornea and cutaneous sensibility. *Experimental Neurology*, **1**, 334–359.

MAGLADERY, J. W. and TEASDALL, R. D. (1961) Corneal reflexes: an electromyographic study in man. *Archives of Neurology, Chicago*, **5**, 269–274.

MOFFIE, D. (1971) Late results of bulbar trigeminal tractotomy. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 270–274.

OLIVER, L. C. (1952) The supranuclear arc of the corneal reflex. *Acta Psychiatrica Scandinavica*, **27**, 329–333.

ONGERBOER DE VISSER, B. W. and GOOR, C. (1974) Electromyographic and reflex study in idiopathic and symptomic trigeminal neuralgias. Latency of the jaw and the blink reflexes. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 1225–1230.

—— —— (1976*a*). Jaw reflexes and masseter myograms in mesencephalic and pontine lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, **39**, 90–92.

—— —— (1976*b*) Cutaneous silent period in masseter muscles: a clinical and electrodiagnostic evaluation. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 674–679.

ONGERBOER DE VISSER, B. W. and KUYPERS, H. G. J. M. (1978) Late blink reflex changes in lateral medullary lesions: an electrophysiological and neuro-anatomical study of Wallenberg's syndrome. *Brain*, **101**, 285-294.

—— MECHELSE, K. and MEGENS, P. H. A. (1977) Corneal reflex latency in trigeminal nerve lesions. *Neurology, Minneapolis*, **27**, 1164-1167.

ROSS, R. T. (1972) Corneal reflex in hemisphere disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 877-880.

ROWBOTHAM, G. F. (1939) Observations of the effects of trigeminal denervation. *Brain*, **62**, 364-380.

RUSHWORTH, G. (1962) Observations on blink reflexes. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 93-108.

SJÖQUIST, O. (1938) Studies on pain conduction in the trigeminal nerve. *Acta Psychiatrica Scandinavica*, Suppl. **17**, 1-139.

SMYTH, G. E. (1939) The systemization and central connections of the spinal tract and nucleus of the trigeminal nerve. *Brain*, **62**, 41-87.

TOWER, S. S. (1940) Unit for sensory reception in cornea. *Journal of Neurophysiology*, **3**, 486-500.

WINDLE, W. F. (1926) The distribution and probable significance of unmyelinated nerve fibres in the trigeminal nerve of cat. *Journal of Comparative Neurology*, **41**, 453-477.

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UNILATERAL NEGLECT, REPRESENTATIONAL SCHEMA AND CONSCIOUSNESS

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INTRODUCTION

THEORIES of unilateral neglect cluster into three main groups, these being classified by reference to the level of function to which one chooses to allocate the disorder from which the behavioural manifestations proceed. First, some authors have argued that the syndrome is the result of an interruption, attenuation, or lack of synthesis in the flow of information conveyed to one hemisphere. The study by Denny-Brown, Meyer and Horenstein (1952) is the most representative of such stimulus-bound theories, among which can also be found Bender's explanation in terms of extinction phenomena (*see* Bender, 1977, for a comprehensive account). On the same (physiological) level, unilateral neglect has more recently been regarded as the one-sided breakdown of mechanisms subserving the 'orienting response' to incoming stimulations (*see* Heilman and Watson, 1977). These theories evolved contemporaneously with a second and different approach, which took into account the representational map which underlies the organization of perceptions and actions: the concept of 'body schema' so insistently referred to in the literature on unilateral neglect is a classical instance thereof. A third, psychodynamic, line of reasoning suggests motivational explanations for some phenomena of the syndrome (Zingerle, 1913; Schilder, 1935; Weinstein and Kahn, 1955). The plausibility of hypotheses of this third kind will not be argued here.

Physiological theories owe much of their appeal to the apparent 'objectiveness' of the mechanisms to which unilateral neglect is reduced; they seemingly dispense with the need to resort to dubious psychological constructs like 'body schema', 'representational space', etc. The concept of body schema was introduced into clinical neurology at the beginning of the century (Wernicke, 1900; Hartmann, 1902; Bonnier, 1905; Pick, 1908; and others) and was subsequently developed by Head and Holmes (1911). Since then it has often been invoked as a clue to the understanding of manifold neurological disorders, including unilateral neglect (Brain, 1941; Gerstmann, 1942; Lhermitte, 1942;

Roth, 1949; Critchley, 1953; and others). As such, however, its force was in most instances not compelling, so that it could be easily disregarded by upholders of other theories. Some reasons for this weakness may be pointed out. Even in Head and Holmes' classical formulation, the structure and function of the schema are far from being exhaustively and unambiguously described. Multiple corporeal schemata are postulated, of which the unifying principle remains obscure. It is not even clear what changes, if any, are to be expected in the schemata after interruption of the sensory inflow at various levels. Subsequent analyses (Lhermitte, 1942) failed to bring major improvements to the concept. A feature common to all these attempts at interpreting the syndrome of unilateral neglect in terms of a disordered schema, and which appears to account for their limited usefulness, is a certain reluctance to enlarge the analysis beyond mere corporeal representation. This is all the more striking when one remembers that conspicuous disorders of behaviour in extra-corporeal hemi-space are no less characteristic of the syndrome than the neglect of one half of the body. But the chief fault of schema-inspired accounts of unilateral neglect is, perhaps, that they have generally misused the concept of schema to *describe* a set of disorders, rather than arguing its necessity as an *explanatory* construct. Though at an advantage conferred by the relative weakness of psychological interpretations, physiological theories are also open to criticism. Denny-Brown *et al.* (1952) for instance, having epitomized the features of the sensory defect ensuing from the parietal lesion of their patient, concluded that 'the very striking change in the general behaviour of the patient, namely her failure to attend to the left side of her body or of space can also be viewed as a disturbance of synthesis of multiple sensory data'. The supposed causal relationship between sensory disorders and unilateral neglect, however, is objectionable on both logical and empirical grounds: loss of information, in fact, does not imply cessation of the search for information, and it is undeniable that sensory disorders at any level do not, as a rule, appear in association with neglect phenomena. Though more satisfactory, the explanation in terms of 'orienting response' which was suggested by Heilman and Watson (1977) fails, like all physiological theories, to account for some of the most essential features of the syndrome. None of these theories are indeed of much use when faced with facts such as the defective blind exploration of the neglected hemi-space by the contralateral, unaffected hand (De Renzi, Faglioni and Scotti, 1970), or the one-sided omission of details from verbal descriptions of remembered scenes (Bisiach and Luzzatti, 1978).

We now present a new piece of evidence which undermines those theories which seek to explain unilateral neglect in terms of a diagram of input-output connectivities. In our opinion this evidence also helps towards an improved conception of the essential structure of the central 'representational schema' whose disorder results in unilateral neglect. Our experiments show that in patients with unilateral brain lesions, forms reconstructed by the temporal integration of successive visual stimuli appearing in a stationary, vertical slit are neglected unilaterally.

As the investigation was primarily addressed to unilateral neglect *per se*, leaving aside the question of inter-hemispheric differences, and in order to avoid any complication by aphasia, the study was restricted to patients with right-sided brain damage.

MATERIALS AND METHODS

Subjects

The subjects of the experiment were 19 right brain-damaged patients showing signs of unilateral neglect (fig. 1). In order to qualify for selection the subjects had to satisfy the following criteria: (*a*) clinical and instrumental evidence of a lesion confined to the right hemisphere, and (*b*) one or more left-sided omissions in crossing out 13 circles in a 23 × 18 cm display. The circles, three in each quadrant, had a diameter of 1 cm and were symmetrically arranged around a central one, which formed the starting point of the task. Three patients were suffering from a brain tumour (C.P., A.C. and A.G.); the other 16 had recently sustained a cerebrovascular attack. Fig. 1 shows the locus and extent of the lesions reconstructed from CT scans (Luzzatti, Scotti and Gattoni, 1979); the data of two of the patients are missing as they were admitted to another hospital. With the exception of V.P., all the patients had a left hemiparesis and a left somatosensory disorder ranging from mild to severe. All had a more or less severe left visual field defect, detected on confrontation. Ocular movements on verbal command, ocular tracking movements and optokinetic nystagmus were examined in 16 of the patients (the missing data are those of T.M., E.G. and M.Z.); they were variously disordered in all these patients except V.P., G.B. and V.M. The control group was formed by 30 patients without past or present evidence of any disease involving the nervous system above the cervical cord. The mean age was 66.40 ± 6.00 years in the brain-damaged patients and 64.58 ± 7.88 in the controls.

Stimuli and Procedure

The subjects were required to detect differences occurring within pairs of patterns successively presented at intervals. These were random, white cloud-like shapes, 20 cm wide and 6 cm high, lying on a blue background. A central sector 10 cm wide was common to all patterns, while the left and right lateral sectors were varied, thus forming three identical pairs, three pairs differing on the left, and three on the right. Nine more pairs were obtained by mirror reversal. Stimuli were presented by means of a Fairchild Mark VI Super-8 Sound Projector placed approximately 50 cm in front of the subject.

In the first part of the experiment (*static* exposure), each pattern figuring a pair was shown for 2 s with a 1 s black interstimulus interval. The 18 pairs followed one another at 5 s intervals. In the second part (*dynamic* exposure), the screen was blacked out with the exception of a central vertical 1.5 × 12 cm slit, which allowed a partial view of the stimulus at each moment. The patterns moved from left to right, or vice versa, at a speed of 10 cm per second. The complete transit of a single pattern behind the slit took, therefore, 2 s. The second pattern of the pair, moving in the same direction as the former, started its transit after a 1 s interstimulus interval. Each of the 18 pairs of stimuli were shown in both left- and rightward motion (*non*-contiguous trials, that is, the rightward transit of a given pair did not follow immediately on the leftward transit of that pair), hence the second part of the experiment consisted of 36 trials, with 5 s intertrial intervals. In both parts of the experiment, pairs of patterns were arranged to follow a fixed, random schedule. Care was, however, taken to ascertain that trials differing on the left and trials differing on the right would not cluster, thus eliminating the possibility of spurious right-left gradients of difference-detections due to fatigue. Subjects were not asked to specify on which side the detected differences occurred. Responses were recorded after each trial and subjects were not informed as to their accuracy.

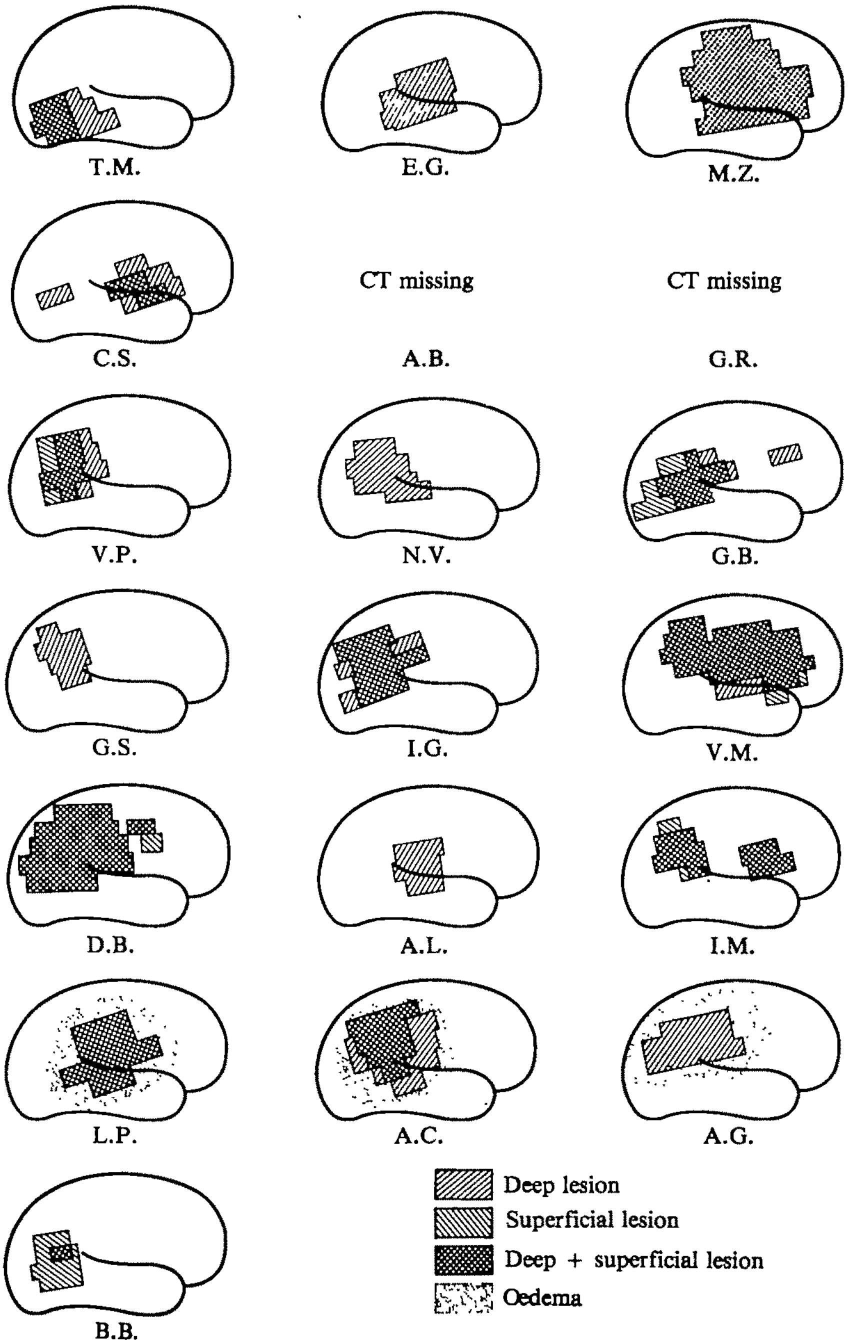

FIG. 1. Locus and extent of lesions in brain-damaged patients. Maps reconstructed from CT scans (Luzzatti *et al.*, 1979).

RESULTS

In Table 1 the scores of correct difference-detections on the left (DDL) and on the right side (DDR) of static patterns are shown. The right-left gradient (DDR-DDL) was found to differ significantly between the patients and the control group (t (47) = 6.26, $P < 0.0001$). The data related to dynamic patterns are shown in Table 2, where separate scores for left- and rightward trials are given. From these scores, the effects of Side, Recency and Direction of the patterns' movement were calculated as shown in Table 3. A 3-variate, one-way analysis of variance (Anderson, 1958) showed that the overall between-groups difference due to these effects was significant (F (3, 45) = 3.338, $P = 0.027$). Multiple comparisons were therefore carried out in order to test the three effects separately (Roy and Bose, 1953; this method yields theta-points derived from the generalized beta-distribution, which

TABLE 1. STATIC PATTERNS
Mean DDL and DDR

Group	*DDL**	*DDR**
Control	3.60	4.10
Brain-damaged	1.37	4.58

* Maximum scores = 6.00.

TABLE 2. DYNAMIC PATTERNS
Mean DDL and DDR in Left- and Rightward Conditions

Group	*DDL** *Leftw.*	*DDL** *Rightw.*	*DDR** *Leftw.*	*DDR** *Rightw.*
Control	2.40	3.40	3.20	2.40
Brain-damaged	1.58	2.47	3.10	2.16

* Maximum scores = 6.00.

TABLE 3. DYNAMIC PATTERNS
Effect of Side, Recency and Direction of Movement on the Detection of Differences

Group	*Side*[1]	*Recency*[2]	*Direction of Movement*[3]
Control	−0.20	+1.80	+0.20
Brain-damaged	+1.21	+1.83	−0.05

[1] (DDR leftw. + DDR rightw.) − (DDL leftw. + DDR rightw.).
[2] (DDL rightw. + DDR leftw.) − (DDL leftw. + DDR rightw.).
[3] (DDL rightw. + DDR rightw.) − (DDL leftw. + DDR leftw.).

could here be converted into points of the F-distribution). The effect of Side was thus found to be significantly different in controls and brain-damaged patients (F (3, 45) = 3.097, $P = 0.036$) whereas the differences concerning the other two effects were far from being significant (F (3, 45) < 1).

DISCUSSION

We begin by making some preliminary remarks with regard to dynamic patterns. Differences on the left halves of these patterns were more apt to be overlooked by our patients than by subjects in the control group: an overall left/right gradient of performance is apparent in the patients, even if in the case of rightward moving patterns this is counteracted by the strong recency effect, which affected equally the performance of both patients and controls. Actually, the patients scored better on the left, rather than the right half of rightward moving patterns (the former being the last half perceived) but it is important to notice that the difference is not as pronounced as in controls. Oculomotor disorders were present in 81.24 per cent of our patients, a finding which is in agreement with Hécaen's (1962) data on the association of these disorders with unilateral neglect. The hypothesis that oculomotor disturbances might somehow have affected the performance of our patients seems to lack validity as the effect of the direction of moving patterns is negligible. This hypothesis is further undermined by the fact that in the three patients who did not show oculomotor disorders the mean Side effect (+1.00) was of the same order as that found in the entire group of patients.

Taking all this into consideration, it would appear to be reasonably safe to make a further analysis of the experimental results in terms of unilateral neglect. Though the data of dynamic patterns can better develop our argument, we think that even the most obvious phenomena of unilateral neglect as those witnessed in the first part of the experiment would claim the primary explanatory role of a representational disorder. This would, however, require the assumptions that (*a*) the nervous system cannot conceivably be programmed to gather information without recruiting an inner model of the source thereof, and (*b*) that any *unmonitored* failure in performing the programme implies a breakdown of the model itself. To state this in simpler terms, we think that in the cases of patients like ours the loss of sensory information about one side of space could be easily remedied through exploratory activity initiated by the intact neural structures, if all *expectations* relative to that side of space were not lacking as a result of the lesion. The incorrigibility of this state even by external pressures, which can be observed in most pronounced cases of unilateral neglect, would suggest that the left side of space has not disappeared from consciousness owing to an *Amnesie der linken Seite* (Zingerle, 1913). On the contrary, we would suggest that in these instances the actual possibility of conceptualizing the existence of a left side is in fact precluded. In any case, a primary disorder of the spatial schema subtending mental representations is self-evident in the second part of the experiment. All spatial features of the patterns shown in the first part were in fact simultaneously displayed and invariant throughout the time of each individual exposure. Some of them might fall into the unattended visual field of brain-damaged patients and be neglected. By contrast the same configurations, when appearing behind the slit, were delineated by a narrow, ever-changing section. Instead of a direct, isomorphic (at least in its earliest stages), neural correlate of their entire shape, it is conceivable that under these viewing conditions, a temporally structured pattern of excitation took place in those formations which subserve vision in proximity to the vertical meridian of the visual field. In order to perceive a moving cloud under these conditions it becomes necessary to effect a translation from an objective temporal dimension into a representational spatial one. Our findings suggest that also the left side of this kind of graph drawn in a merely representational space may to some extent fade into unilateral neglect. It is worth emphasizing that under these viewing conditions no inattention to parts of stimuli occurs and that unilateral neglect affects the internal representations of these stimuli manifesting itself in the left side of the reconstructed cloud, irrespective of whether this side refers to its leading or trailing edge. A topological relationship, therefore, seems to link to the neural substrate the spatial schema where these percepts take shape.

The same conclusion had been reached with reference to left-sided omissions from verbal descriptions of remembered perspectives (Bisiach and Luzzatti, 1978). Hence it is likely that the same spatial schema is involved in the two instances, even though the source of the processed information is different.

Pylyshyn (1973) has warned against possible misuses of the phenomenological concept of 'image' as an explanatory construct in psychological theories. He states that visual representations are 'much closer to being a description of the scene than a picture of it'. None the less, our findings suggest that the spatial attributes of representations cannot be accounted for solely in terms of propositional retrieval: their *left* side fades in consequence of *right* hemisphere impairment, so that their spatial schema appears to be mapped across the brain. Non-localizationistic views of conscious brain activity, of which one of the most intriguing up-to-date developments is holographic models (Pribram, 1971, 1972, 1977; Pribram, Nuwer and Baron, 1974), must face the weight of this evidence afforded by unilateral neglect, even though the major manifestations of the latter are so amazingly ephemeral. Finally, the crucial share of the right hemisphere in the structuring of the representational schema in question does not support existing claims which by mistaking consciousness as being the ability to communicate the contents thereof verbally confine it to the left hemisphere of the brain (Eccles, 1976; Popper and Eccles, 1977; Weimer, 1977).

On a more general ground, it is not possible in our opinion to accommodate the data in question by interactionistic theories of mind (*see* Popper and Eccles, 1977). A mind, not co-extensive with part of the brain, would of necessity be endowed with its own invulnerable model of the world if it were to be able to read out from nervous activity and act on it coherently. Accordingly, it would not endorse the oblivion of one side of the world, even less that of the representational world. On the contrary, it would counteract oblivion by resorting immediately to the surviving neural structures, which would be potentially quite adequate to overcome the defect. This is, in fact, the interactionist's expectation, as expressed by Popper: '. . . the liaison brain is, as it were, almost an object of choice of the self-conscious mind. That is to say, if a certain part of the brain is not available, the self-conscious mind will seek another part as substitute.' (loc. cit., p. 495) which is refuted by the syndrome of unilateral neglect.

SUMMARY

Right brain-damaged patients with unilateral neglect were asked to detect differences within pairs of patterns moving left- or rightward behind a narrow vertical slit. It was seen that differences occurring on the left side of the mentally reconstructed images were less easily detected; therefore it is suggested that a representational disorder plays a primary role in unilateral neglect. In the light of these findings, it is possible to take into consideration some implications of unilateral neglect for theories of conscious brain activity.

ACKNOWLEDGEMENT

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REFERENCES

ANDERSON, T. W. (1958) *An Introduction to Multivariate Statistical Analysis.* New York: John Wiley.

BENDER, M. B. (1977) Extinction and other patterns of sensory interaction. In: *Hemi-inattention and Hemisphere Specialization.* Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 107-110.

BISIACH, E. and LUZZATTI, C. (1978) Unilateral neglect of representational space. *Cortex,* **14,** 129-133.

BONNIER, P. (1905) L'aschématie. *Revue Neurologique,* **12,** 605-609.

BRAIN, W. R. (1941) Visual disorientation with special reference to lesions of the right cerebral hemisphere. *Brain,* **64,** 244-272.

CRITCHLEY, M. (1953) *The Parietal Lobes.* New York: Hafner.

DENNY-BROWN, D., MEYER, J. S. and HORENSTEIN, S. (1952) The significance of perceptual rivalry resulting from parietal lesion. *Brain,* **75,** 433-471.

DE RENZI, E., FAGLIONI, P. and SCOTTI, G. (1970) Hemispheric contribution to exploration of space through the visual and tactile modality. *Cortex,* **4,** 191-203.

ECCLES, J. C. (1976) Brain and free will. In: *Consciousness and the Brain.* Edited by G. G. Globus, G. Maxwell and I. Savodnik. New York: Plenum Press, pp. 101-121.

GERSTMANN, J. (1942) Problem of imperception of disease and of impaired body territories with organic lesions. *Archives of Neurology and Psychiatry*, **48**, 890–913.

HARTMANN, F. (1902) Quoted by H. Zingerle.

HEAD, H. and HOLMES, G. (1911) Sensory disturbances from cerebral lesions. *Brain*, **34**, 102–254.

HÉCAEN, H. (1962) Clinical symptomatology in right and left hemispheric lesions. In: *Interhemispheric Relations and Cerebral Dominance*. Baltimore: Johns Hopkins Press, pp. 215–243.

HEILMAN, K. M. and WATSON, R. T. (1977) The neglect syndrome—a unilateral defect of the orienting response. In: *Lateralization in the Nervous System*. Edited by S. Harnad, R. W. Doty, L. Goldstein, J. Jaynes and G. Krauthamer. New York: Academic Press, pp. 285–302.

LHERMITTE, M. J. (1942) De l'image corporelle. *Revue Neurologique*, **74**, 20–38.

LUZZATTI, C., SCOTTI, G. and GATTONI, A. (1979) Further suggestion for intracranial localization. *Cortex*. In press.

PICK, A. (1908) Quoted by Friedland, R. P. and Weinstein, E. A. (1977). In: *Hemi-inattention and Hemisphere Specialization*. Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 1–31.

POPPER, K. R. and ECCLES, J. C. (1977) *The Self and Its Brain*. Berlin: Springer.

PRIBRAM, K. H. (1971) *Languages of the Brain: Experimental Paradoxes and Principles in Neuropsychology*. Englewood Cliffs, New Jersey: Prentice-Hall.

—— (1972) Some dimensions of remembering: Steps toward a neuropsychological model of memory. In: *Macromolecules and Behavior*. Edited by J. Gaito. New York: Appleton-Century-Crofts, Chapter 17.

—— (1977) Some comments on the nature of the perceived universe. In: *Perceiving, Acting and Knowing*. Edited by R. Shaw and J. Bransford. Hillsdale, New Jersey: Lawrence Erlbaum, pp. 83–101.

—— NUWER, M. and BARON, R. (1974) The holographic hypothesis of memory structure in brain function and perception. In: *Contemporary Developments in Mathematical Psychology*. Edited by R. C. Atkinson, D. H. Krantz, R. C. Luce and P. Suppes. San Francisco: Freeman, pp. 416–457.

PYLYSHYN, Z. W. (1973) What the mind's eye tells the mind's brain: A critique of mental imagery. *Psychological Bulletin*, **80**, 1–24.

ROTH, M. (1949) Disorders of the body image caused by lesions of the right parietal lobe. *Brain*, **72**, 89–111.

ROY, S. N. and BOSE, R. C. (1953) Simultaneous confidence interval estimation. *Annals of Mathematical Statistics*, **24**, 513–536.

SCHILDER, P. (1953) Quoted by Friedland, R. P. and Weinstein, E. A. (1977). In: *Hemi-inattention and Hemisphere Specialization*. Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 1–31.

WEIMER, W. B. (1977) A conceptual framework for cognitive psychology: Motor theories of mind. In: *Perceiving, Acting and Knowing*. Edited by R. Shaw and J. Bransford. Hillsdale, New Jersey: Lawrence Erlbaum, pp. 267-311.

WEINSTEIN, E. A. and KAHN, R. L. (1955) *Denial of Illness*. Springfield, Illinois: Charles C. Thomas.

WERNICKE, K. (1900) Quoted by Zingerle, H. (1913).

ZINGERLE, H. (1913) Ueber Stoerungen der Wahrnehmung des eigenen Koerpers bei organischen Gehirnerkrankungen. *Monatschrift für Psychiatrie und Neurologie*, **34**, 13-36.

(*Received June 22, 1978*)

Brain (1979), **102**, 619–635

THE CARPAL TUNNEL SYNDROME

LOCALIZATION OF CONDUCTION ABNORMALITIES WITHIN THE DISTAL SEGMENT OF THE MEDIAN NERVE[1]

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INTRODUCTION

THE carpal tunnel syndrome (CTS) has been extensively studied electrophysiologically (Simpson, 1956; Gilliatt and Sears, 1958; Lambert, 1962; Kaeser, 1963; Phalen, 1966; Thomas, Lambert and Cseuz, 1967; Melvin, Schuchmann and Lanese, 1973; Duensing, Lowitzsch, Thorwirth and Vogel, 1974). When testing a patient for this syndrome it is customary to measure the motor latency of the median nerve from the wrist to the muscle and the sensory latency from the digit to the wrist. More recently, however, methods have been described to determine the conduction time in the segment across the carpal tunnel. For this purpose, the motor axons may be stimulated not only at the wrist but also at the palm to activate the median innervated thenar muscles (Roth, 1970). For the sensory axons the digital nerve may be stimulated to record the orthodromic sensory potential at the palm and wrist (Wiederholt, 1970*a*; Buchthal and Rosenfalck, 1971), or alternatively, the nerve may be stimulated at the wrist and palm and the digital potential recorded antidromically (Kimura, 1978).

Buchthal, Rosenfalck and Trojaborg (1974), and Daube (1977), studying orthodromic sensory conduction, clearly demonstrated that electrophysiological abnormalities in the CTS were often limited to the wrist-to-palm segment of the median nerve. A subsequent study using palmar stimulation also showed focal slowing under the transverse carpal ligament for both sensory and motor axons in 13 patients with the CTS (Kimura, 1978). To further localize the point of maximal conduction delay in the CTS, 105 additional patients have now been studied with stimulation of the median nerve not only at midpalm but also at multiple sites across the carpal tunnel. The results will be compared to a similar study on surgically exposed median nerves (Brown, Ferguson, Jones and Yates, 1976) and to experimental work on entrapment neuropathy with sharply localized demyelination at the edges of compression (Ochoa, Fowler and Gilliatt, 1972; Ochoa and Marotte, 1973). The present series also confirms the clinical value of palmar stimulation as a diagnostic test of the CTS (Roth, 1970; Daube, 1977; Kimura, 1978).

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[1] This work was presented in part at the Sixth International Congress of Electromyography, Stockholm, Sweden, June 17, 1979.

METHODS

All studies were done with the subject supine in a warm room with the temperature maintained at 26 to 28° C. Skin temperatures were checked over the forearm and, if necessary, the limbs were warmed with an infra-red heat lamp to maintain the temperature at 34° C or greater.

Based on the previously described anatomical course (Robbins, 1963; Johnson and Shrewsbury, 1970) the median nerve was stimulated percutaneously at 12 points between midpalm and the distal forearm in 1 cm increments. As shown in fig. 1, the zero level represented the proximal edge of the transverse carpal ligament and was at the distal crease of the wrist (Robbins, 1963). Each stimulus point was indicated by the distance in centimetres from the zero level assigning a '−' sign distally. The distal edge of the transverse carpal ligament then lay at or close to the '−3' level (Johnson and Shrewsbury, 1970). An additional stimulus was given at the elbow on the anterior surface of the upper arm over the brachial pulse. At each stimulus site the anode was 2 cm proximal to the cathode and the ground electrode was placed around the forearm.

In determining the origin of the thenar nerve at the palm, however, the anode was placed distally rather than proximally to the cathode. This reversal of electrode position was necessary since otherwise (Kimura, 1978) the thenar nerve was sometimes activated near the anode due to spread of stimulating current even if the cathode was clearly distal to the origin of the nerve. A surface distance measured to the cathodal point would then overestimate the nerve length, thereby resulting in an erroneously fast motor nerve conduction velocity. The stimulating electrodes were moved in small increments from the distal palm towards the wrist until an appropriate thumb twitch appeared, indicating that the cathode was just over the origin of the thenar nerve. In most subjects, the median innervated thenar muscles were first activated at '−3' or '−4' level, that is near the distal edge of the transverse carpal ligament (Johnson and Shrewsbury, 1970). Stimulation further distally either failed to produce a twitch or caused adduction of the thumb with activation of a deep branch of the ulnar nerve.

The compound muscle action potential was recorded with electrodes placed over the belly of the abductor pollicis brevis (G1) and its tendon (G2) just distal to the metacarpophalangeal joint. The sensory nerve action potential was recorded antidromically with ring electrodes placed around the proximal (G1) and distal (G2) interphalangeal joints of the second digit. At least two trials were given at each stimulus site to confirm the consistency of the response. Shock intensity was gradually advanced until a further increase no longer altered the size of sensory nerve or muscle potential. A specially designed amplifier with short blocking time (1.0 ms) and low noise (0.5 μV RMS at bandwidth of 2000 Hz) was developed to overcome the problems of stimulus artefact (Walker and Kimura, 1978). Frequency response used was 20 to 2000 Hz for sensory nerve and 20 to 32000 Hz for muscle action potentials.

For both sensory nerve and muscle action potentials, latencies were measured in steps of 0.1 ms from the stimulus artefact to the onset of the initial negative response (upward deflection). The amplitude was determined from the baseline to the negative peak. In studying the mixed nerve, the antidromically recorded sensory potential may be obscured by superposition of action potentials from distal muscles since some motor axons have a threshold similar to that of the large myelinated sensory axons. In the present study, therefore, sensory fibres were selectively activated with palmar stimulation distal to the origin of the recurrent motor fibres. Moving more proximally, possible superposition of muscle action potential was easily recognized by a change in wave-form of the elicited response. Meaningful assessments of focal conduction abnormalities depended upon the accuracy in determining latency of serially elicited sensory nerve potentials. Certain precautions taken to achieve this goal will be briefly described below.

In symptomatic hands, serial stimulation was conducted only in those selected primarily for the ease in eliciting sensory potential with stimulation at the wrist. Some of these hands were further excluded when calculating latency changes in 1 cm increments because responses were either absent or equivocal at one or more stimulus sites along the palmar branch. Even with the selected group, the localized increase in sensory conduction time was often associated with some reduction in amplitude.

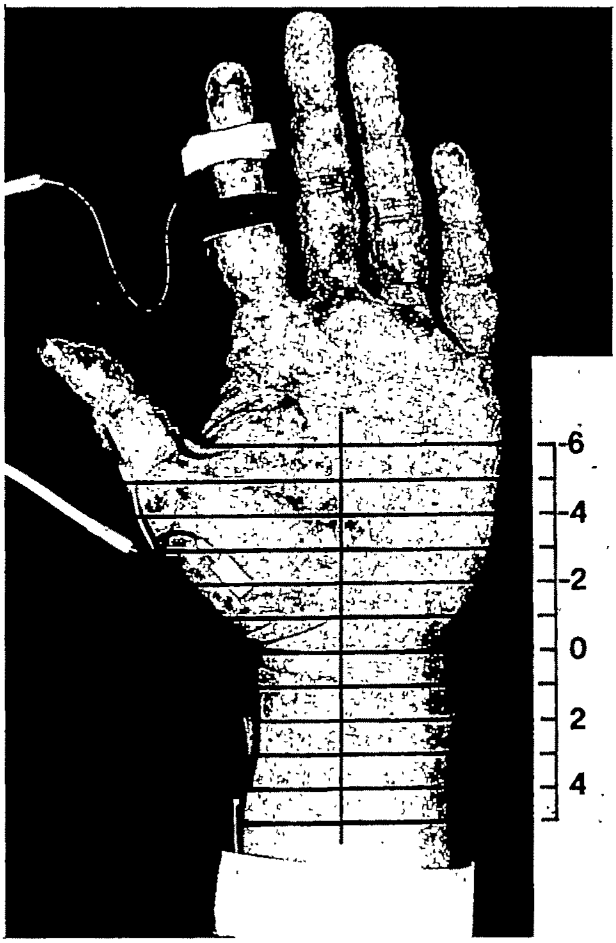

FIG. 1. Twelve sites of stimulation in 1 cm increments along the length of the median nerve. The '0' level was at the distal crease of the wrist, corresponding to the origin of the transverse carpal ligament. Sensory nerve and muscle action potentials were recorded from the second digit and abductor pollicis brevis, respectively.

None the less, onset latency measured to a corresponding point of each sensory potential could be determined with considerable accuracy if a series of eight responses were displayed simultaneously rather than individually with step-wise vertical shift of the baseline as shown in fig. 2. When a marker was positioned to the desired spot of the wave-form the latency was automatically displayed digitally, further reducing possible error in measurement.

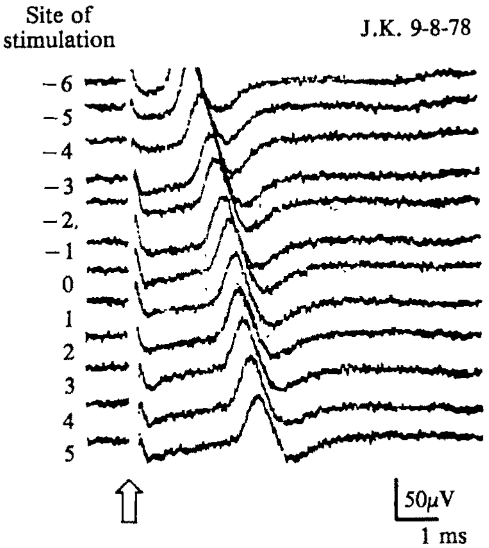

FIG. 2. Sensory nerve potentials in a normal subject recorded after stimulation of the median nerve at multiple points across the wrist. The site of each stimulus is indicated on the left (*see* fig. 1). The latency increased linearly as the stimulus site was moved proximally in 1 cm increments.

If the onset latency was not sufficiently clear, the peak latency was used as a point of reference. In normal hands, latency increase of sensory potential from one stimulus to the next was nearly the same whether it was measured to the onset or to the peak. This was also the case in most symptomatic hands, the exception being a double humped potential seen in a few subjects at the point of localized slowing. With simultaneous display of serial responses, an imaginary line connecting successive peaks was nearly linear in normals. A disproportionate latency increase exceeding 0.5 ms/cm was readily detectable by discontinuation of this line at the point of localized conduction delay (figs. 3-8). Hence, a focal slowing of the nerve was arbitrarily defined as conduction time exceeding 0.5 ms/cm and more than twice that of the other 1 cm segments. Focal abnormalities fulfilling the criteria were such that minor errors in latency determination would have altered the outcome of the study very little. In fact, the number of patients with localized slowing was the same whether the data were analysed using 0.1 ms or 0.2 ms steps.

Sensory and motor nerve conduction time across the carpal tunnel were determined as the latency difference between the two evoked potentials elicited with stimulation at the wrist and palm. For this purpose the stimulus site at the wrist was 3 cm proximal to the distal crease of the forearm ('3'). Palmar stimulation was applied 5 cm distally ('−5') for sensory axons and at the most distal point eliciting contraction of the median nerve innervated thenar muscles for motor axons ('−3' or '−4').

Sensory and motor nerve conduction velocities (SNCV and MNCV) in the wrist-to-palm segment were determined according to the conventional formula by dividing the distance by the latency difference. For the motor axons, however, this segment was short (5 to 7 cm) and the exact site of nerve activation by palmar stimulation was uncertain. In assessing motor conduction abnormalities across the carpal tunnel, therefore, the latency difference rather than MNCV was primarily used to avoid possible errors in estimating the short nerve length by surface measurement. The SNCV for the palm-to-digit segment was determined by dividing the surface distance from midpalm to the proximal interphalangeal joint (G1) by the latency of the nerve potential recorded with palmar stimulation.

MATERIALS AND RESULTS

1. *Normal Values*

Normal values were established in 122 hands from 61 patients with complaints unrelated to the carpal tunnel syndrome. All subjects were examined to exclude polyneuropathies and other disorders of the median nerve. There were 26 men and 35 women ranging in age from 15 to 50 years (average age 43 years).

Serial stimulation in 1 cm increments increased the sensory latency almost linearly as the stimulus site was moved proximally (figs. 2 and 3). However, the latency increase was slightly but significantly ($P < 0.01$) greater from '−4' to '−3' (0.22±0.10 ms), '−3' to '−2' (0.20±0.09 ms) and '−2' to '−1' (0.19±0.08 ms) compared to the adjacent distal segment from '−5' to '−4' (0.17±0.08 ms) or proximal segment from '−1' to '0' (0.16±0.08 ms). There was no statistically significant difference

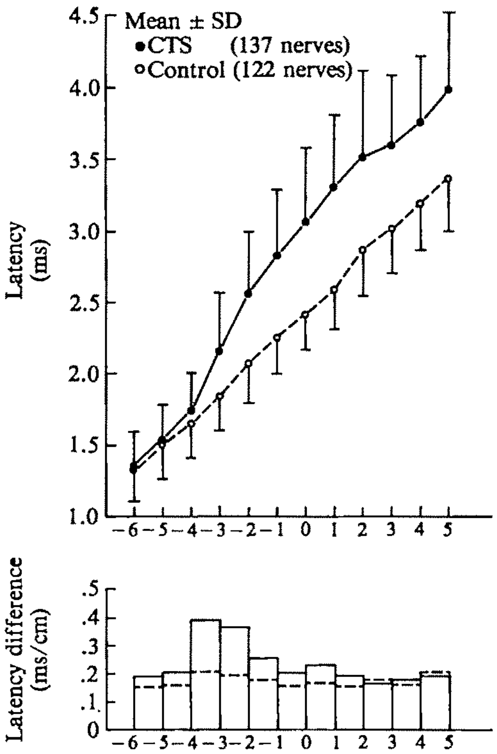

FIG. 3. Sensory latency after stimulation of the median nerve in 1 cm increments across the wrist (*top*) and conduction times over successive 1 cm segments (*bottom*) in the carpal tunnel syndrome and control group. The sites of stimulation are shown on the abscissa (*see* fig. 1) and time in ms, on the ordinate. The 1 cm segments with maximal conduction delay were located 2 to 4 cm distally to the origin of the transverse carpal ligament ('0') in the carpal tunnel syndrome, and to a much lesser extent, in the control group.

between successive 1 cm segments in the remaining more distal or proximal segments. Unlike the sensory axons the motor axons did not always show consistent latency changes per cm distal to the '−1' level. Indeed, the motor latency not uncommonly decreased as the stimulus site was moved proximally in the palm, presumably because stimulation intended for the median nerve proper near the wrist activated the recurrent thenar branch near the motor point, resulting in an erroneously short latency. In these cases, carefully placing the stimulation electrode away from the thenar eminence was helpful but not always successful in eliminating the problem. Serial stimulation proximal to the '−1' level, however, showed a linear latency increase, ranging from 0.19 to 0.25 ms/cm.

TABLE 1. CONTROL SUBJECTS (MEAN ± SD)

	Nerve segments tested	*Amplitude (mV for motor, μV for sensory)*	*Latency (ms)*	*Latency difference (ms)*	*Conduction velocity (m/s)*
Motor fibres:	Palm	7.6 ± 3.2	2.11 ± 0.31	1.50 ± 0.21	49.0 ± 5.7
122 hands from	Wrist	6.6 ± 2.6	3.60 ± 0.36	3.86 ± 0.48	59.0 ± 5.0
61 control subjects	Elbow	6.5 ± 2.5	7.46 ± 0.67		
Sensory fibres:	Digit				58.1 ± 7.7
122 hands from	Palm	44.8 ± 22.0	1.41 ± 0.22	1.41 ± 0.18	57.3 ± 6.9
61 control subjects	Wrist	41.3 ± 19.3	2.82 ± 0.28	3.58 ± 0.50	63.2 ± 6.3
	Elbow	30.9 ± 14.8	6.41 ± 0.66		

The wrist-to-digit segment was bisected into two approximately equal portions by midpalmar stimulation. Thus, there was no significant difference in sensory latency between the wrist-to-palm and remaining more distal segments (Table 1). The motor latency, however, was considerably greater ($P < 0.001$) in the palm-to-muscle segment than in the wrist-to-palm segment, presumably because of a delay at the neuromuscular junction. Hence, the latency ratio of the wrist-to-palm segment to the remaining distal portion was significantly smaller for motor (mean ± SD: 0.73 ± 0.15) than sensory axons (1.02 ± 0.02). The SNCV was the same in the wrist-to-palm and palm-to-digit segments but was significantly faster between the elbow and wrist ($P < 0.001$). The MNCV was also significantly faster for the proximal segment above the wrist than for the wrist-to-palm segment ($P < 0.001$). The antidromically activated sensory nerve potential was largest when the nerve was stimulated at midpalm and smallest when stimulated at the elbow with a statistical difference only between wrist and elbow ($P < 0.001$). There was no significant difference in amplitude of the muscle action potential regardless of the site of stimulation.

The limits of normal were defined as the mean plus or minus two standard deviations in the control group. Thus, the sensory latency was considered abnormal if it exceeded 3.4 ms for wrist-to-digit, 1.8 ms for wrist-to-palm, and 1.9 ms for palm-to-digit segment. The upper limit of normal for the motor latency was 4.4 ms for wrist-to-muscle, 2.0 ms for wrist-to-palm and 2.8 ms for palm-to-muscle segments. The SNCV was considered slow if it was less than 50 m/s from elbow to wrist, 43 m/s from wrist-to-palm, and 42 m/s from palm to digit, and the MNCV, if it was less than 49 m/s from elbow to wrist and 37 m/s from wrist to palm.

2. *Carpal Tunnel Syndrome*

From January to October 1978 105 patients with the carpal tunnel syndrome were studied in our laboratory. All had typical but relatively mild signs associated with entrapment of the median nerve at the wrist, unilaterally or bilaterally. Most had the onset of symptoms within a few months before the test. Patients were excluded if a polyneuropathy was clinically suspected even if a superimposed carpal tunnel syndrome was likely. Inclusion in the study was based on the clinical impression and not on the results of nerve conduction studies. There were 32 men and 73 women ranging in age from 20 to 78 years (average age 48 years). Each patient was tested on both sides but the clinically affected hands were analysed separately from the asymptomatic hands (Table 2). There were 172 symptomatic hands, 134 from 67 patients affected bilaterally and 38 from the remaining patients with unilateral disease, 29 on the right and 9 on the left.

TABLE 2. PATIENTS WITH THE CARPAL TUNNEL SYNDROME (MEAN±SD)

	Nerve segments tested	*Amplitude (mV for motor, μV for sensory)*	*Latency (ms)*	*Latency difference (ms)*	*Conduction velocity (m/s)*
Motor fibres:	Palm	6.1±3.2	2.15±0.34	2.79±0.93	28.2±7.5
172 hands from	Wrist	5.3±2.9	4.94±1.03	4.04±0.58	55.5±6.4
105 patients	Elbow	5.0±2.7	8.99±1.17		
Sensory fibres:	Digit				53.9±9.0
172 hands from	Palm	31.3±14.9	1.48±0.28	2.18±0.43	38.5±7.5
105 patients	Wrist	29.3±14.9	3.70±0.59	3.69±0.46	59.7±6.2
	Elbow	23.5±12.5	7.38±0.81		

Serial stimulation of the sensory axons was conducted in 137 hands with relatively well preserved sensory potentials (fig. 3). In 18 of these, there was no abnormality in the wrist-to-palm segment. In 28 others the sensory nerve potential could not be elicited at one or more stimulus sites, the response commonly being absent at the '−2' to '−4' levels. In 44 (48 per cent) of the remaining 91 symptomatic hands conduction abnormalities were evenly distributed along the wrist-to-palm segment (fig. 4). In the other 47 (52 per cent) symptomatic hands, there was a sharply localized abnormality over a 1 cm segment (conduction time exceeding 0.5 ms/cm and more than twice that of the other 1 cm segments). Of the 47 hands, the maximal conduction delay was between '−6' to '−5' in 1, '−4' to '−3' in 22, '−3' to '−2' in 17 and '−2' to '−1' in 5 and at two separate levels in 2 (figs. 5–8). In these hands, the focal latency change across the affected 1 cm segment (0.80±0.22 ms/cm) averaged more than four times that of the adjacent distal (0.19±0.09 ms/cm) or proximal 1 cm segment (0.19±0.08 ms/cm). A disproportionate latency increase per centimetre from one stimulus point to the next was often associated with a distinct change in wave-form (figs. 5–8). Sensory symptoms were subjective and difficult to quantitate, but there was no apparent relationship between their severity and the presence of a localized slowing.

As in the control patients, the motor latency was difficult to test serially over the wrist-to-palm segment. Thus it was often impossible to determine accurately the area of maximal motor conduction delay within the wrist-to-palm segment. In a few affected hands, however, there was a disproportionate latency increase per 1 cm segment at or proximal to the '−1' level with a considerably smaller change in the adjoining distal or proximal 1 cm segments (figs. 6–8). This finding was taken to indicate a localized slowing of motor axons since, in normals, serial stimulation in 1 cm increments increased motor latency linearly at these levels. It is of interest that in these hands, sensory and motor axons were not necessarily slowed to the same degree, nor were they always affected at the same level. The discrepancy may be because the recurrent motor fibres are often contained in a separate channel in the carpal ligament.

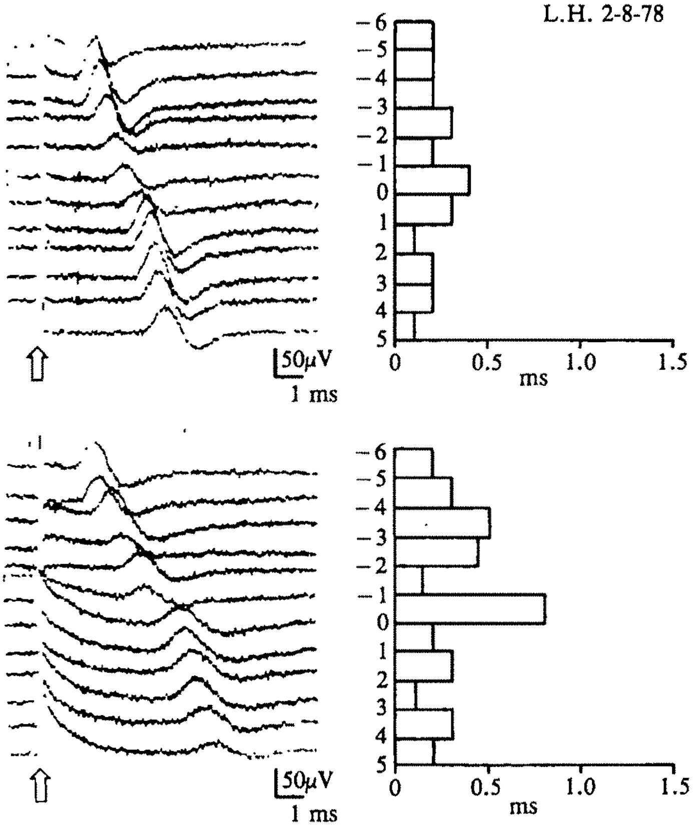

FIG. 4. Sensory nerve potentials of the left (*top*) and right (*bottom*) hands in a patient with the carpal tunnel syndrome. The histogram on right shows the conduction time over successive 1 cm segments. The site of each stimulus is indicated on the ordinate and the conduction time on the abscissa. In both hands, conduction abnormalities were distributed fairly evenly along the length of the nerve with no 1 cm segment showing a change more than twice of the other 1 cm segments.

Of the 172 clinically affected nerves the sensory nerve potential was absent in 23 and the muscle action potential in 5 with stimulation either at midpalm or wrist. Thus, there were 149 sensory and 167 motor axons available for analysis of nerve conduction studies (Table 2). Latencies were considerably greater and conduction velocities smaller in the CTS than in the controls over the wrist-to-palm segment ($P < 0.001$). In the remaining distal segment there was no difference between the two groups for motor axons and only a small difference for the sensory axons ($P < 0.05$). In the carpal tunnel syndromes, unlike in the controls, the latency across the carpal tunnel was greater than that in the palm-to-wrist or palm-to-muscle segments ($P < 0.001$). Thus, the latency ratio between the two segments was abnormally increased for both motor (mean ± SD: 1.32 ± 0.46) and sensory axons (1.50 ± 0.44). The evoked responses were significantly smaller in amplitude than the corresponding normal values regardless of the site of stimulation for both sensory nerve and muscle action potentials ($P < 0.001$). In the carpal tunnel syndromes amplitude of muscle potentials was significantly larger when elicited by stimulation at palm as compared to wrist or elbow ($P < 0.02$). There was no statistical difference in amplitude of sensory nerve potentials at palm and wrist

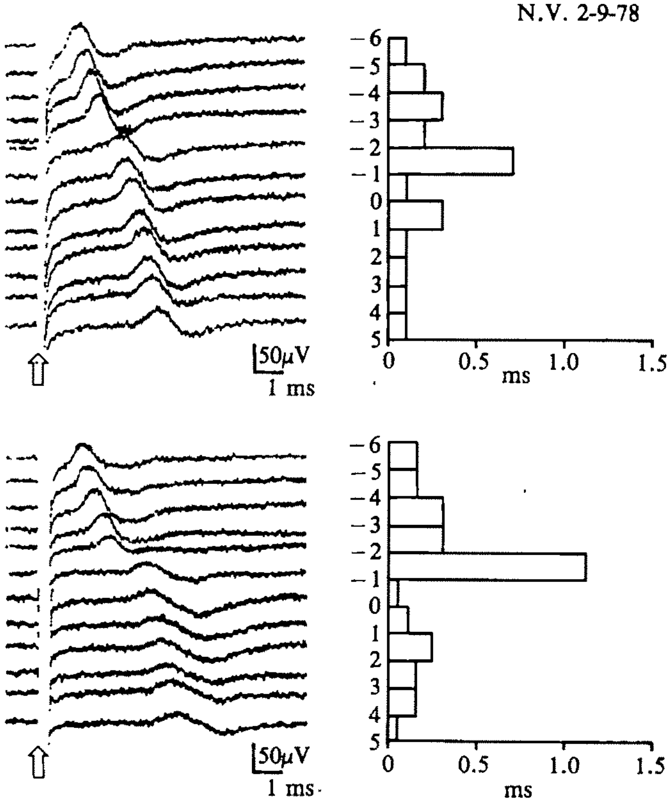

FIG. 5. Sensory nerve potentials in a patient with the carpal tunnel syndrome. The arrangement is the same as for fig. 4. A sharply localized slowing was found from '−2' to '−1' in both hands, representing a maximum conduction velocity of 14 m/s on the left (*top*) and 9 m/s on the right (*bottom*). Note a distinct change in wave-form of the sensory potential at the point of localized conduction delay. Double humped appearance at '−2' on the left suggests sparing of some sensory axons at this level.

($P > 0.1$), but the response elicited with stimulation at the elbow was significantly smaller ($P < 0.001$).

Based solely on the conventional wrist-to-digit latency, abnormalities of sensory conduction were found in 108 (63 per cent) of 172 symptomatic hands. Palmar stimulation revealed slowed SNCV across the carpal tunnel in 36 (21 per cent) additional hands. The motor conduction was abnormal on the basis of the conventional wrist-to-muscle latency in 105 (61 per cent) hands. An additional 40 (23 per cent) hands were considered abnormal after palmar stimulation. The sensory conduction across the wrist-to-palm segment was slow when the motor conduction was normal in 16 hands but the reverse was true in 19 hands. Taking both motor and sensory conduction studies into consideration, electrophysiological abnormalities were found in all but 13 (8 per cent) symptomatic hands. Had it not been for palmar stimulation, however, an additional 32 (19 per cent) hands with clinical signs would have been regarded as normal. In 4 of these, the wrist-to-palm latencies were within normal limits but there was a focal slowing of sensory conduction greater than 0.5 ms per 1 cm segment, across '−4' to '−3' in 2 and '−3' to '−2' in the others.

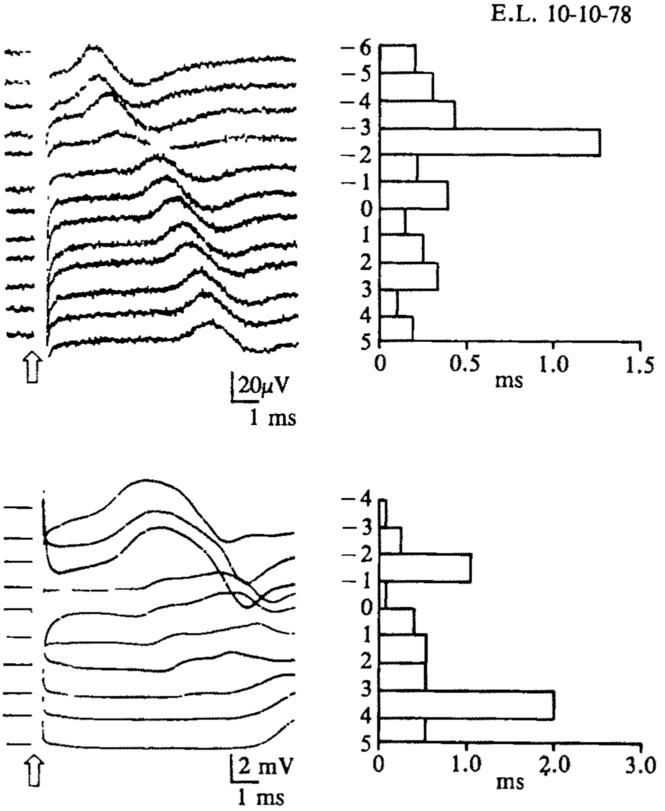

FIG. 6. Sensory nerve (*top*) and muscle action potentials (*bottom*) in a symptomatic hand with the carpal tunnel syndrome. The arrangement is similar to fig. 4 except for a different time scale on the abscissa for motor latencies. There were localized slowings from '−3' to '−2' for sensory and from '−2' to '−1' and from '3' to '4' for motor axons.

DISCUSSION

Studies of experimental acute pressure neuropathy and chronic entrapment neuropathy in the guinea pig have stressed the importance of mechanical factors (Fullerton and Gilliatt, 1967; Ochoa *et al.*, 1972; Ochoa and Marotte, 1973; Rudge, Ochoa and Gilliatt, 1974). In these studies the area of maximal histological abnormalities were under the edges of the compressed regions, which could only be explained as a result of a mechanical agent and not on the basis of ischæmia (Denny-Brown and Brenner, 1944*a*, *b*). Brown *et al.* (1976) determined the conduction time of 0.5 cm segments by direct stimulation of the exposed median nerve during operation for the carpal tunnel syndrome. Of 23 affected median nerves the 0.5 cm segment having the maximum motor conduction time was proximal to the transverse carpal ligament in 4, within 2 cm distally in 15, and beyond 2 cm distally in 4. A focal increase in the conduction time over a 0.5 cm

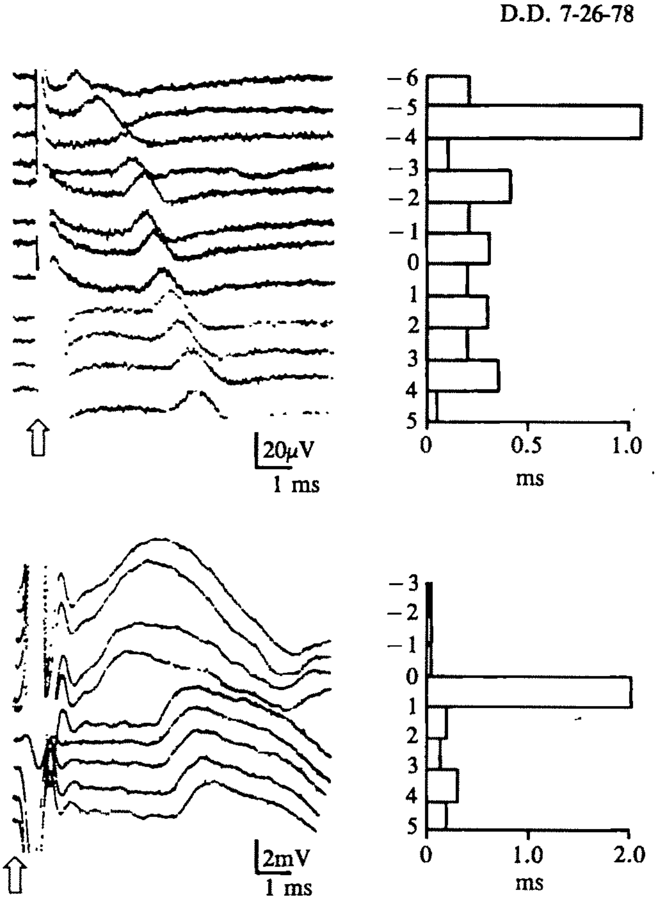

FIG. 7. Sensory nerve (*top*) and muscle action potentials (*bottom*) in a symptomatic hand with the carpal tunnel syndrome. The arrangement is the same as for fig. 6. A sharply localized slowing is seen from '−5' to '−4' for sensory and from '0' to '1' for motor axons.

segment of the nerve was noted in 6 but the abnormal increase was more evenly distributed along the length of the nerve in the remaining 17 hands.

A larger group of patients was tested in the present series using a non-invasive technique to localize the point of maximal conduction delay in the carpal tunnel syndrome. The use of a fast recovery amplifier improved the accuracy of measuring nerve conduction over short segments by controlling the stimulus artefact (Walker and Kimura, 1978). Using percutaneous stimulation, it is sometimes difficult to determine the exact point of nerve activation because of possible spread of stimulating current (Wiederholt, 1970*b*). In our material, however, the sensory latencies were reproducible from one trial to the next, provided that care was taken to use just maximal shock intensity at each stimulus site. Moreover, the sensory latency increased linearly as the stimulus site was

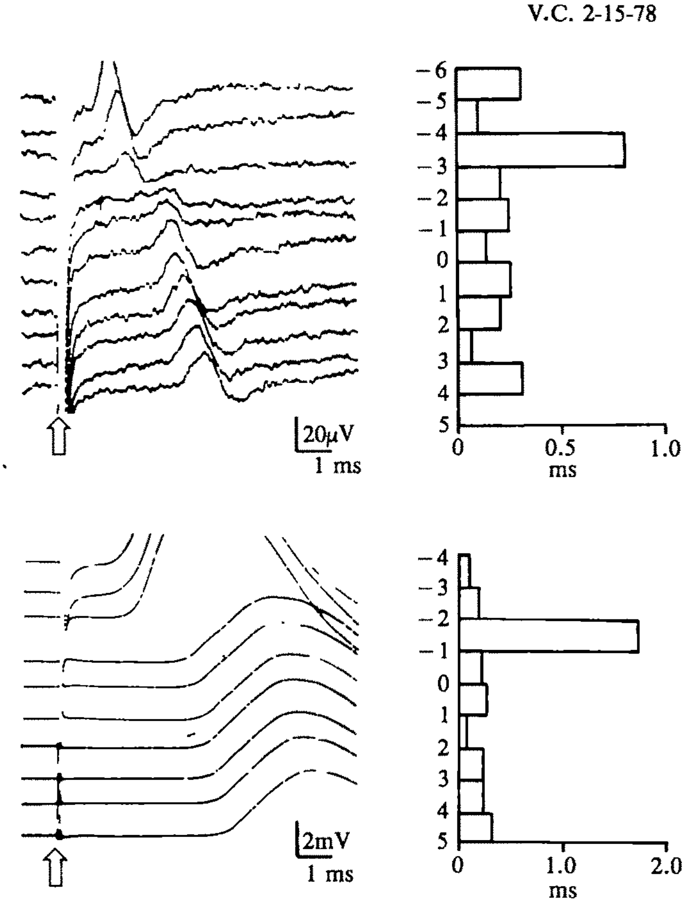

FIG. 8. Sensory nerve (*top*) and muscle action potentials (*bottom*) in a symptomatic hand with the carpal tunnel syndrome. The arrangement is the same as for fig. 6. There were localized slowings from '−4' to '−3' for sensory and from '−2' to '−1' for motor axons. Note a temporally dispersed, double peaked sensory nerve potential at the point of localized conduction delay ('−3').

moved proximally in normal hands as well as in unaffected portions of the symptomatic hands, indicating that the current spread was either negligible or similar at different sites of stimulation. This finding gave a rationale for determining the conduction time over 1 cm segments as latency differences between successive sensory nerve potentials. None the less, the possibility still remained that a stimulus applied over a severely affected nerve segment might have activated the adjacent proximal or distal portion which was less diseased and consequently more readily excitable.

A focal increase in the sensory conduction time was noted in 52 per cent of the affected hands tested serially. The location of the 1 cm segment having the maximal conduction time was usually 2 to 4 cm distal to the distal crease of the wrist although in a few exceptional cases focal involvement was noted in unusual positions including the segment proximal to the wrist. A sharply localized slowing was by no means the rule since in 48 per cent of the affected nerves, abnormalities were distributed more evenly across the carpal tunnel. There were no anatomical data available in the present series to substantiate the exact location of lesions relative to the transverse carpal ligament. Using the well established surface landmarks (Robbins, 1963; Johnson and Shrewsbury, 1970), however, our results suggest that abnormalities abound at or close to the distal edge of this ligament (fig. 3).

The present findings are consistent with the sharply localized abnormalities found under both distal and proximal edges in experimental acute and chronic compression neuropathy (Ochoa *et al.*, 1972; Ochoa and Marotte, 1973). Severe conduction block of sensory and motor fibres localized to the presumed lower margin of the compression was also described in human pneumatic tourniquet paralysis (Bolton and McFarlane, 1978). Anatomical studies suggest that the smallest cross-sectional area within the carpal tunnel is found 2.0 to 2.5 cm distal to the entrance where the tunnel is rigidly bound on three sides by bony structures and roofed by a thickened transverse carpal ligament (Robbins, 1963). Interestingly, the location of the 1 cm segment with maximal conduction time was also found 2 to 4 cm distally to the origin of the ligament in the control group. Thus, mild involvement of the median nerve may be present at this particular level in some of the clinically asymptomatic hands. Neary, Ochoa and Gilliatt (1975) have shown such focal abnormalities in 5 of 12 median nerves at routine autopsy from patients without known disease of the median nerve (*also see* Gilliatt, 1978).

In contrast with direct stimulation of the exposed nerves (Brown *et al.*, 1976), it was not possible to activate the motor axons in steps of 1 cm with any consistency by percutaneous stimulation. This is presumably because of the recurrent course of the thenar nerve which branches off the median nerve proper in a separate tunnel near the distal edge of the transverse carpal ligament (Johnson and Shrewsbury, 1970). If one stimulus is inadvertently misdirected to a terminal portion of the thenar nerve and another, delivered 1 cm proximally, activates only the median nerve trunk, an unreasonably large latency increase occurs between the two stimuli thereby presenting a fallacious impression of focal slowing. To avoid the same sort of error in the calculation of motor latency over the wrist-to-palm segment it is essential to select carefully the most distal point of palmar stimulation eliciting an appropriate thumb twitch. One can then be reasonably certain that palmar stimulation activated the median nerve at or near the origin of the thenar nerve as intended. This problem is further compounded because the recurrent branch may take an anomalous course in rare instances (Werschkul, 1977).

The present results in the carpal tunnel syndromes confirm relatively selective slowing of sensory and motor conduction within the wrist-to-palm segment (Buchthal *et al.*, 1974; Daube, 1977; Kimura, 1978). Since the conduction abnormalities were often limited to this segment, the exclusion of the normal distal segment made it possible to demonstrate a mild conduction delay across the involved segment. Indeed a disproportionate latency increase was present over a 1 cm segment in four hands even when the overall conduction time in the longer wrist-to-palm segment showed little significant change. Histological and electrophysiological changes in the motor axons of the forearm were previously described in association with median nerve compression at the wrist in animals (Anderson, Fullerton, Gilliatt and Hern, 1970) as well as in man (Thomas and Fullerton, 1963; Buchthal *et al.*, 1974). This was the case in some but not many of our patients who had relatively mild disease. In agreement with previous studies (Buchthal *et al.*, 1974; Kimura, 1978) the sensory axons were rarely affected in the segment above the wrist. The average MNCV and SNCV over the elbow-to-wrist segment, however, were significantly ($P < 0.001$) slower in the carpal tunnel syndromes than in the control group.

According to Sunderland (1968), one of the characteristic features of tourniquet paralysis is the susceptibility of the motor fibres in that they are the first to fail, the last to recover, and in the mildest lesions, may be the only ones to suffer. In previous work on the carpal tunnel syndrome (Kaeser, 1963; Phalen, 1966; Thomas *et al.*, 1967; Buchthal and Rosenfalck, 1971; Melvin *et al.*, 1973; Buchthal *et al.*, 1974; Duensing *et al.*, 1974), however, motor conduction testing was generally considered less sensitive than studies of the sensory axons. This was not true in the present series where abnormalities were evenly distributed between the sensory and motor axons. In fact motor conductions were sometimes selectively affected while sensory conductions remained normal, although the reverse was also seen. In some of the previous studies the sensory axons were tested in the palm-to-wrist segment excluding the digit-to-palm portion whereas the motor axons were studied in the wrist-to-muscle segment. Thus, the lesser sensitivity of motor conduction studies might well have been because the normal palm-to-muscle segment masked a mild slowing across the carpal tunnel (Roth, 1970). The present findings suggest that studies of motor and sensory conduction across the carpal tunnel are supplementary to each other in early detection of a mild carpal tunnel syndrome.

The use of palmar stimulation also provides a simple means to establish whether the slowing of sensory or motor conduction is attributable to compression by the transverse carpal ligament or to a disease process of the most terminal segment. This distinction is potentially important in differentiating the carpal tunnel syndrome from a distal neuropathy in which the median nerve may be more intensely affected in the terminal portions, as shown by Casey and Le Quesne (1972) who studied digital nerves in diabetics. In a few patients with early diabetic polyneuropathy studied in our laboratory the segment distal to the palm was significantly affected with essentially normal SNCV and MNCV in the more proximal segments including the wrist-to-palm portion. Further studies are necessary in a larger number of patients to establish the patterns of conduction abnormalities in polyneuropathies as compared to the compression syndrome. It is suggested, however, that the assessment of the terminal portion of the median nerve distal to the transverse carpal ligament is a useful addition to the conventional nerve conduction studies in localizing the area of maximal involvement. The technique may be used not only as a diagnostic test but also for evaluation of the underlying pathophysiology of various median nerve neuropathies.

SUMMARY

Palmar stimulation was used to assess median nerve conduction across the carpal tunnel in 61 control patients and 105 patients with the carpal tunnel syndrome. With serial stimulation from midpalm to distal forearm the sensory axons normally showed a predictable latency change of 0.16 to 0.21 ms/cm as the stimulus site was moved proximally in 1 cm increments. In 47 (52 per cent) of 91 affected nerves tested serially, there was a sharply localized latency increase across a 1 cm segment, most commonly 2 to 4 cm distally to the origin of the transverse carpal ligament. In these hands, the focal latency change across the affected 1 cm segment (mean ± SD: 0.80 ± 0.22 ms/cm) averaged more than four times that of the adjoining distal (0.19 ± 0.09 ms/cm) or proximal 1 cm segments (0.19 ± 0.08 ms/cm). In the remaining 44 (48 per cent) hands, the latency increase was distributed more evenly across the carpal tunnel. Unlike the sensory axons the motor axons were difficult to test serially because of the recurrent course of the thenar nerve, which may be contained in a separate tunnel.

The wrist-to-palm latency was significantly greater in the patients with carpal tunnel syndromes than in the controls for sensory (2.18 ± 0.48 ms v 1.41 ± 0.18 ms) and motor axons (2.79 ± 0.93 ms v 1.50 ± 0.21 ms). Consequently, there was considerable difference between the carpal tunnel syndromes and controls in SNCV (38.5 ± 7.5 m/s v 57.3 ± 6.9 m/s), and MNCV (28.2 ± 7.5 m/s v 49.0 ± 5.7 m/s). In the remaining distal segment, however, there was only a small difference between the two groups in sensory (1.48 ± 0.28 ms v 1.41 ± 0.22 ms) and motor latency (2.15 ± 0.34 ms v 2.10 ± 0.31 ms). The exclusion of the relatively normal distal latency made it possible to demonstrate mild slowing across the carpal tunnel in 36 (21 per cent) sensory and 40 (23 per cent) motor axons of 172 affected nerves when the conventional terminal latencies were normal. Sensory or motor conduction abnormalities were found in all but 13 (8 per cent) hands. Without palmar stimulation, however, an additional 32 (19 per cent) hands would have been regarded as normal.

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REFERENCES

ANDERSON, M. H., FULLERTON, P. M., GILLIATT, R. W. and HERN, J. E. C. (1970) Changes in the forearm associated with median nerve compression at the wrist in the guinea-pig. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 70–79.

BOLTON, C. F. and McFARLANE, R. M. (1978) Human pneumatic tourniquet paralysis. *Neurology, Minneapolis*, **28**, 787–793.

BROWN, W. F., FERGUSON, G. G., JONES, M. W. and YATES, S. K. (1976) The location of conduction abnormalities in human entrapment neuropathies. *Canadian Journal of Neurological Sciences*, **3**, 111–122.

BUCHTHAL, F. and ROSENFALCK, A. (1971) Sensory conduction from digit to palm and from palm to wrist in the carpal tunnel syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 243–252.

—— —— and TROJABORG, W. (1974) Electrophysiological findings in entrapment of the median nerve at wrist and elbow. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 340–360.

CASEY, E. B. and LE QUESNE, P. M. (1972) Digital nerve action potentials in healthy subjects, and in carpal tunnel and diabetic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 612–623.

DAUBE, J. R. (1977) Percutaneous palmar median nerve stimulation for carpal tunnel syndrome. *Electroencephalography and Clinical Neurophysiology*, **43**, 139–140 (abstract).

DENNY-BROWN, D. and BRENNER, C. (1944*a*) Paralysis of nerve induced by direct pressure and by tourniquet. *Archives of Neurology and Psychiatry, Chicago*, **51**, 1–26.

—— —— (1944*b*) Lesion in peripheral nerve resulting from compression by spring clip. *Archives of Neurology and Psychiatry, Chicago*, **52**, 1–19.

DUENSING, F., LOWITZSCH, K., THORWIRTH, V. and VOGEL, P. (1974) Neurophysiologische Befunde beim Karpaltunnelsyndrom. *Zeitschrift für Neurologie*, **206**, 267–284.

FULLERTON, P. M. and GILLIATT, R. W. (1967) Median and ulnar neuropathy in the guinea-pig. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**, 393–402.

GILLIATT, R. W. (1978) Sensory conduction studies in the early recognition of nerve disorders. *Muscle and Nerve*, **1**, 352–359.

—— and SEARS, T. A. (1958) Sensory nerve action potentials in patients with peripheral nerve lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **21**, 109–118.

JOHNSON, R. K. and SHREWSBURY, M. M. (1970) Anatomical course of the thenar branch of the median nerve—usually in a separate tunnel through the transverse carpal ligament. *Journal of Bone and Joint Surgery*, **52-A**, 269–273.

KAESER, H. E. (1963) Diagnostische Probleme beim Karpaltunnelsyndrom. *Deutsche Zeitschrift für Nervenheilkunde (Berlin)*, **185**, 453–470.

KIMURA, J. (1978) A method for determining median nerve conduction velocity across the carpal tunnel. *Journal oj Neurological Sciences*, **35**, 1–10.

LAMBERT, E. H. (1962) Diagnostic value of electrical stimulation of motor nerve. *Electroencephalography and Clinical Neurophysiology* (Suppl.), **22**, 9–16.

MELVIN, J. L., SCHUCHMANN, J. A. and LANESE, R. R. (1973) Diagnostic specificity of motor and sensory nerve conduction variables in the carpal tunnel syndrome. *Archives of Physical Medicine and Rehabilitation*, **54,** 69–74.

NEARY, D., OCHOA, J. and GILLIATT, R. W. (1975) Sub-clinical entrapment neuropathy in man. *Journal of Neurological Sciences*, **24,** 283–298.

OCHOA, J., FOWLER, T. J. and GILLIATT, R. W. (1972) Anatomical changes in peripheral nerves compressed by pneumatic torniquest. *Journal of Anatomy*, **113,** 433–455.

—— and MAROTTE, L. (1973) The nature of the nerve lesion caused by chronic entrapment in the guinea-pig. *Journal of Neurological Sciences*, **19,** 491–495.

PHALEN, G. S. (1966) The carpal tunnel syndrome, seventeen years' experience in diagnosis and treatment of six hundred and fifty-four hands. *Journal of Bone and Joint Surgery*, **48-A,** 211–228.

ROBBINS, H. (1963) Anatomical study of the median nerve in the carpal tunnel and etiologies of the carpal tunnel syndrome. *Journal of Bone and Joint Surgery*, **45-A,** 953–966.

ROTH, G. (1970) Vitesse de conduction motrice du nerf median dans le canal carpien. *Annales de Médecine Physique*, **13,** 117–132.

RUDGE, P., OCHOA, J. and GILLIATT, R. W. (1974) Acute peripheral nerve compression in the baboon. *Journal of Neurological Sciences*, **23,** 403–420.

SIMPSON, J. A. (1956) Electrical signs in the diagnosis of carpal tunnel and related syndromes. *Journal of Neurology, Neurosurgery and Psychiatry*, **19,** 275–280.

SUNDERLAND, S. (1968) *Nerves and Nerve Injuries.* Baltimore: Williams and Wilkins, pp. 140–142.

THOMAS, J. E., LAMBERT, E. H. and CSEUZ, K. A. (1967) Electrodiagnostic aspects of the carpal tunnel syndrome. *Archives of Neurology, Chicago*, **16,** 635–641.

THOMAS, P. K. and FULLERTON, P. M. (1963) Nerve fibre size in the carpal tunnel syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **26,** 520–527.

WALKER, D. D. and KIMURA, J. (1978) A fast-recovery electrode amplifier for electrophysiology. *Electroencephalography and Clinical Neurophysiology*, **45,** 789–792.

WERSCHKUL, J. D. (1977) Anomalous course of the recurrent motor branch of the median nerve in a patient with carpal tunnel syndrome. *Journal of Neurosurgery*, **47,** 113–114.

WIEDERHOLT, W. C. (1970*a*) Median nerve conduction velocity in sensory fibers through carpal tunnel. *Archives of Physical Medicine and Rehabilitation*, **51,** 328–330.

—— (1970*b*) Threshold and conduction velocity in isolated mixed mammalian nerves. *Neurology, Minneapolis*, **20,** 347–352.

(*Received January 9, 1979*)

Brain (1979), **102**, 637–650

NOTICES OF RECENT PUBLICATIONS

Movements of the Eyes. By R. H. S. CARPENTER, 1977. Pp. 420. London: Pion (distributed by Academic Press, London and New York). Price £13·50.

R. H. S. Carpenter's book on eye movements fills a very real need in oculomotor physiology. It is well written by an author with a broad command of the literature and an appreciation of the need for functional interpretations of experimental results in the context of control systems analysis. The book is primarily aimed at the undergraduate or beginning graduate student who, with a rather elementary knowledge of physiology, would like a summary of our state of knowledge in the field of eye movements. It will also be useful to those in related research areas (for instance, motor neurophysiology) who want to keep abreast of developments in oculomotor control and to those who might wish to incorporate such material in a course, for example, on cybernetics or perceptual psychology. Even experts in the field will find it a handy source of references. The expert will, of course, not find much that he does not already know. The book is not aimed at such an audience and the size of the book precludes treatment of any of the subject matter in great detail.

Until Carpenter's book appeared there had been, oddly enough, no textbook at all on the physiology and neurophysiology of eye movements. The need of such a book became increasingly obvious as the literature on the subject grew by leaps and bounds in the last ten years since it became possible to record from oculomotor pathways in alert animals. Oculomotor neurophysiology has become one of the most rapidly growing branches of neurophysiology today (certainly so in motor neurophysiology) yet its progress has been recorded in fragments in symposia proceedings and journals which cover such diverse topics as neurophysiology, cybernetics, psychology and clinical neuro-ophthalmology. Carpenter saw this need and filled it. Since his book is the only one on this topic so far (others are sure to follow) its very existence, good or bad, fills a pedagogic vacuum. The reference list alone forms a valuable reading guide for the student. Fortunately, Carpenter's book is also clearly and thoughtfully written and so performs its function well.

Carpenter is to be congratulated on avoiding an approach common in neurophysiology and neuroanatomy, in which a large amount of information is presented with many references but in which there is little attempt to explain what it all means from a functional standpoint. He seeks the teleological approach. Eye movements obviously accomplish some purpose and unless one understands that purpose, intelligent interpretation of experimental results is impossible. Knowledge of anatomical connections, and whether a post-synaptic potential is excitatory or inhibitory or mono- or oligo-synaptic is interesting, from a hardware standpoint but is of moderate, or only potential importance, unless it sheds light on how signals are being processed to achieve the presumptive function of a given system. The emphasis of Carpenter's book indicates this attitude. Anatomical and intracellular electrophysiological results (usually from non-alert animals) are given when they appear useful to the reader in understanding how some system might work but are glossed over lightly or ignored when they would add little to functional interpretations. Thus, the electrophysiologist and anatomist will be disappointed by the treatment of such subject matter in this book.

Accompanying this functional approach, Carpenter appropriately uses control systems analysis throughout. For many years (until the mid-1960s when recordings of ocular motor-command signals became possible), progress in oculomotor physiology was mainly limited to new knowledge of the system's hardware. What had been missing and is now no longer missing, was how brain-stem and cerebellar signal processing performed the operations that permitted proper control of an eye movement. This knowledge allows one to formulate theoretical hypotheses of eye movement control, the predictions of which can be tested by future, guided experiments. This activity, called modelling, is impossible to do with systems of even modest complexity without using such elementary notions as block diagrams, transfer functions, time and frequency domain responses and feedback theory. As time goes on it will be increasingly difficult to understand the control system which governs eye movements without understanding something of the analytical methods of control systems in general. While a student who is unfamiliar with such concepts can still obtain an overview of oculomotor physiology from this book, Carpenter also makes it clear by example that a lack of these tools can limit one, not in understanding oculomotor hardware, but in understanding oculomotor control.

Carpenter is not currently active in oculomotor research. His one excursion in this field, reported in 1972, concerned the effect of cerebellectomy on the vestibulo-ocular reflex. This evidently led to an enthusiasm for the subject matter, a command of the literature and an awareness of the void created by the lack of any book on the subject. To write such a book requires more that one be able to make an intelligent appraisal of the available information than to actually be active in the field. In fact, a bit of distance between the appraiser and the battleground of laboratory research probably allows the author to treat the material in a more objective and even-hand way. The disadvantage of being removed from active research is that one is apt to miss the underground currents of thought to be found in unpublished observations and the backroom conversations that go on in laboratories and at meetings. Of course, any book on a subject growing as rapidly as oculomotor neurophysiology is bound to be out of date in just a few years but one can delay the inevitable by being aware of the thinking that will shape ideas and experiments in the next few years to come. In this sense, Carpenter's book is less representative of the state of oculomotor neurophysiology in 1976 than it might have been (*see below*). This does detract a bit from the book's value since, while it does give the beginning student an overview, it is already badly out of date in a number of fairly important matters.

The book divides its subject matter into three broad categories. The first concerns function and describes the properties of various eye movement subsystems. The second concerns structure and deals with the physiology of the muscles, neuroanatomy and the results of lesions, stimulation and recording in various structures in the brain-stem and cerebellum. The third then discusses a variety of special aspects such as the sense of visual direction, saccadic suppression, miniature eye movements and vision, and finally discusses schemes which deal with interactions between all the eye movement subsystems. It is always difficult to organize such a large body of information so as to progress smoothly along direct lines of reasoning. The problem with Carpenter's arrangement is that, for example, anyone interested in the vestibulo-ocular reflex finds its description divided among three major parts of the book and also mentioned in connection with other issues in several other sections. This arrangement of structure and function across systems can seem awkward to someone who thinks in terms of the systems themselves. Often it is difficult to use the book as a quick reference guide to the literature since one may not remember just where in the book a given subject was discussed.

There are two appendices to the book. The first is on methods of measuring eye movements. It is rather sketchy and serves the potential oculomotorist as a guide to the literature rather than offering enough information (for instance, cost, simplicity of construction, accuracy, bandwidth, drawbacks in special circumstances, such as the unco-operative patient, whether the apparatus can be rotated with the subject in testing the vestibulo-ocular reflex) to enable someone to decide which is the best system for a given application. The second appendix is on systems analysis. It is easy to appreciate how an advocate of these techniques yields to the temptation to say to the reader, 'If you do not know these things you should and I will teach them to you here and now'. Unfortunately, those who do not know these things will not really be able to understand let alone use operator theory, which is at the heart of systems analysis, from the necessarily brief treatment given. The best one can hope for is that it will catch the fancy of a few readers so that they will go on to take a proper course in the subject. On the other hand, one wonders if the 56 pages devoted to the two appendices might have been better employed in more fully developing certain areas of oculomotor neurophysiology.

The following discussion focuses on more specific points in the book which I feel do not reflect current thinking. In my view, a major shortcoming in this book is the failure to distinguish between the optokinetic and pursuit systems. They are lumped together as a visual tracking system (Chapter 3). The pursuit system is a visual tracking system peculiar to animals with foveas. The optokinetic system is *not* a visual tracking system and to regard it as such leads to great confusion. It is the low-frequency supplement of the vestibulo-ocular reflex and deals only with the visual consequences of self-rotation in a stable visual surround. This became clear when it was found that optokinetic signals appeared on second-order vestibular neurons (Dichgans, Schmidt and Graf, 1973; Henn, Young and Finley, 1974). This concept has been especially well demonstrated by Waespe and Henn (1977) although that work appeared too late for inclusion in Carpenter's book. These findings explained why the rotation of an enclosing optokinetic drum causes the illusion of self-rotation called circularvection (Brandt, Dichgans and Büchele, 1974; Henn and Young, 1975) and provided a rational basis for optokinetic after-nystagmus and its loss after vestibular apparatus lesions (Uemura and Cohen, 1972; Zee, Yee and Robinson, 1976; Collewijn, 1976; Robinson, 1977*a*, *b*).

Thus, from 1974 on it became increasingly clear that the optokinetic system evolved as a low-frequency supplement to the vestibulo-ocular reflex and was only activated in nature by self-rotation, the only stimulus which causes the entire visual surround to move *en bloc* relative to the subject. The pursuit system has a quite different function: that of holding the image of an object, which is moving against a stationary background, on or near the fovea (for those animals having something similar to a fovea). The properties and dynamics of the two systems are quite different and they may be pitted against each other in many situations. Carpenter has recognized many of the facts regarding each system and cited much of the pertinent literature but appears to regard the two behaviour patterns as produced by a single system.

Attempting to use a single model to describe the behaviours of two such disparate systems is not useful and will serve, unfortunately, to perpetuate a confusion that has existed since 1825 when Purkinjė used the word 'optokinetic' to describe the pursuit movements made by people watching a procession of cavalry. The fault is not Purkinje's since he who invents a term may define it as he likes. The publications of ter Braak in the 1930s indicated that he perceived very well the symbiotic relationship between the optokinetic and vestibular systems but the confusion between the optokinetic and pursuit systems has been perpetuated in both the physiological and clinical literature for many years. It is unfortunate that Carpenter's book will perpetuate it for several more years. This criticism does not pertain to just one or two points in the book, but to all parts of the book which discuss optokinetic and pursuit movements.

Several new developments have occurred in the vestibulo-ocular reflex which do not appear in Carpenter's book. The following findings were emerging from the laboratory in 1973–1975. While most of them had appeared in print only in the form of an abstract, the results were fairly well known to workers in the field and their omission from Carpenter's book probably reflects the fact that he was not active at that time in oculomotor research. Since progress has naturally continued in all these areas of research, I have also included references to further work that appeared after 1975. Two studies on the signals transmitted in the medial longitudinal fasciculus (mlf) were done in 1974 (Davis-King, Lisberger, Fuchs and Evinger, 1974; King, Lisberger and Fuchs, 1976; Pola and Robinson, 1974; Pola and Robinson, 1978). They discovered that the signal sent from the vestibular nucleus via the mlf to the motoneurons of vertical muscles was not just a repetition of the vestibular nerve signal but a complex, half vestibular, half oculomotor signal. This finding has considerably changed current ideas about the signal processing in the vestibulo-ocular reflex and the significance of the concept of the three neuron arc.

Graybiel and Hartwieg (1974) first put horseradish peroxidase in the oculomotor nucleus and discovered a projection from the abducens nucleus. Shortly thereafter, Baker and colleagues (Baker and Highstein, 1975; Delgado-Garcia, Baker and Highstein, 1977) christened these cells internuclear neurons and worked out their electrophysiology while the studies of King *et al.* (1976) and Pola and Robinson (1978) described the signal carried by these fibres in the monkey. These findings are very important in describing the internal workings of the vestibulo-ocular reflex and the results of mlf lesions, known clinically as internuclear ophthalmoplegia. In particular, bilateral lesions of the mlf *do* abolish the vertical vestibulo-ocular reflex and all participation of the medial rectus in this reflex (Evinger, Fuchs and Baker, 1977). These results are entirely consistent with the nature of the signals found flowing in the mlf and must supersede the results of Lorente do Nó (1933) cited by Carpenter. In short, the mlf is essential for the execution of vestibular commands by all the motoneurons in the trochlear and oculomotor nuclei but that tract carries many more oculomotor signals to these neurons than just the vestibular component.

In parallel with the above story, the discovery of projections from the prepositus nucleus to the oculomotor nucleus (Graybiel and Hartwieg, 1974) led to a rapid exploration of the electrophysiology of this circuit (Baker and Berthoz, 1975; *see* Baker, 1977 for a review). This nucleus receives a strong vestibular projection and contains cells with burst-tonic and tonic-pause activity in either vertical or horizontal directions which is sent to ocular motoneurons. Admittedly, we do not yet know the specific function or oculomotor contribution of the prepositus nucleus but it is clearly an important eye movement pathway.

Also in 1973, King (Davis-King and Fuchs, 1973; King and Fuchs, 1977) and Büttner (Büttner, Büttner-Ennever and Henn, 1977) were exploring the region around the oculomotor nucleus (for example, mesencephalic reticular formation, interstitial nucleus of Cajal) in the alert monkey and found a variety of burst and burst-tonic cells. These results provide some important new information about the organization of vertical gaze which will certainly shape our hypotheses in this area for some time to come including the participation of this region in the vestibulo-ocular reflex.

Cells, located in the monkey flocculus, which I call gaze-velocity Purkinje cells, were studied by Lisberger and Fuchs (1974, 1978*a*, *b*) and Miles and Fuller (1975). The modulation of the discharge rate of such cells is not proportional to the velocity of the eye in the head or head in space but to their sum, eye velocity in space, or gaze velocity. It is quite certain that these cells play a very important role in smooth pursuit movements and in cancelling the vestibulo-ocular reflex.

The end result is that Carpenter's treatment of the organization of the vestibulo-ocular reflex (sections 9.1.4 to 9.1.6) is based on rather old data which were rapidly being superseded by new findings in the very years in which he was writing his manuscript. The new findings are far from trivial with the result that Carpenter's book presents a rather obsolete picture of the internal organization of the vestibulo-ocular reflex.

One additional new finding has emerged which appeared too late to be included in Carpenter's book but is worth mentioning. In a model of the optokinetic system (Robinson, 1977*a*, *b*) I pointed out that the existence of circuits associated with the optokinetic system have the important consequence of prolonging vestibular nystagmus in the dark. It is now clear that while the cupula time constant in cat and monkey is 4 and 6 s respectively, the time constant of the slow phase of eye velocity is 12 and 16 s respectively. This transformation had been recognized (Robinson, 1976) but that it took place directly on second-order vestibular neurons (observable only in unanesthetized animals) was described by Buettner, Büttner and Henn (1978). This fact considerably changes our ideas of 'cupulometry' in the sense that the time course of vestibular nystagmus does *not* represent cupula dynamics and a variety of brain-stem lesions may drastically alter the transformation between the latter and the former.

My only comment pertaining to Chapter 8 on the extraocular muscles is that Lennerstrand (1975) had already shown that the muscle fibres innervated by *en grappe* axons, or multi-innervated fibres, consisted of two types one of which responded to stimulation with a twitch, the other responding with a graded contracture (these are types 4 and 5 in the nomenclature of Alvarado and van Horn (1975)). These fibre-types had in common the fact that the frequency of stimulation at which they fused was much lower than the frequency at which they developed maximum tension. While the significance of this fact is not clear, it is the only mechanical difference known between singly- and multi-innervated fibres and must contain a clue to why the latter are found in eye muscles (Robinson, 1978). Thus, Lennerstrand's findings are, in my opinion, the most important, recent contribution to the physiology of extraocular muscles and should have been mentioned in this book.

A few comments might be made on the subject of miniature eye movements. Carpenter reviews the question of whether slow drift can be corrective and points out that one could tell that at once if it were possible to observe long periods of fixation free from microsaccades. Unfortunately, most experiments designed to observe a sort of random walk phenomenon in drift are done in the dark when any drift control system would be without feedback. However, the opportunity to study saccade-free drift occurs in man when subjects are told to stop making microsaccades (Steinman, Haddad, Skavenski and Wyman, 1973), in cats (Winterson and Robinson, 1975), and monkeys (Skavenski, Robinson, Steinman and Timberlake, 1975) which do not make microsaccades (although the latter can be trained to do so). In these cases, the eyes do not drift away from the object of regard. Mean eye position is constant and drifts away from that point are equalized by drifts towards it.

These observations suggest that drift is the result of random central fluctuations which are lessened by a visual feedback that acts on both the position of the retinal error as well as its rate of change—drift velocity. When vision is lost, mean eye position wanders off target and drift velocity increases. While the latter has not been measured for man, drift velocity in rabbit (Collewijn and van der Mark, 1972; Collewijn, Winterson and Dubois, 1978), cat (Winterson and Robinson, 1975), and monkey (Skavenski *et al.*, 1975) rises from about 0.2 deg/s in the light to about 1.0 deg/s in the dark. When microsaccades are permitted, it is possible that they can appear to be corrective or in certain cases even anticorrective but at least it seems clear that eye position can be maintained by a slow visuomotor system which produces drifts that may be considered 'corrective'.

It is now generally thought that it is the slow drifts that keep the perception of retinal images from fading rather than microsaccades. The simplest demonstration of this is the fact that images do not fade when subjects suppress their microsaccades (Steinmann *et al.*, 1973). This does not mean that microsaccades cannot destabilize images—they do—but the work of Gerrits and Vendrik (1974) indicates that they are less efficient at it than the slow drifts. The question may not yet be completely settled and the discrepancies between the later and earlier work with stabilized images remains to be explained, but it would have been appropriate in Carpenter's book to point out the contrary evidence even if one did not agree with the current trend of believing that it is the slow drifts, not the microsaccades that prevent visual fading.

In fact, the function of microsaccades becomes more and more puzzling as one discovers that very little happens when they are dispensed with. Rabbits, of course, do not make them at all. Neither do cats and, as has been mentioned, monkeys normally do not make saccades less than about 0.5 degrees but in a task requiring acuity and vigilance, begin to make frequent saccades in the range down to 5 minutes of arc. However, when naïve human subjects are given a task demanding good acuity (threading a needle, sighting a gun) they make fewer, not more microsaccades (Winterson and Collewijn, 1976). The dynamics of microsaccades are peculiar: usually the first movement is followed at once by a smaller saccade in the opposite direction (called dynamic overshoot). Sometimes a sequence of three saccades occur with no intervening interval. The function, if any, of these wiggles is unknown. Often, the second saccade, in the case of dynamic overshoot, is as large as the first resulting in a negligible net eye displacement. It is very difficult to see what was accomplished by such a movement. While Carpenter does discuss the situation to some extent, he tends to agree in the end with the older literature which concludes that microsaccades keep images from fading and re-centre the image after slow drifts—conclusions which are now seriously doubted.

The above criticisms should not detract from the large amount of well organized information which is to be found in this book and especially in the critical appraisal of results and the attempt to see to what extent the data could be fitted with analytical hypotheses (models). This book will be very useful to the student and novice oculomotorist who can get a broad overview of the system and then, if he wishes, go on into the details and intricacies described in the proceedings of conferences and scientific journals.

DAVID A. ROBINSON

REFERENCES

ALVARADO, J. A. and VAN HORN, C. (1975) Muscle cell types of the cat inferior oblique. In: *Basic Mechanisms of Ocular Motility and Their Clinical Implications.* Edited by G. Lennerstrand and P. Bach-y-Rita. Oxford: Pergamon Press, pp. 15-43.

BAKER, R. (1977) The nucleus prepositus hypoglossi. In: *Eye Movements*: ARVO Symposium. Edited by B. A. Brooks and F. J. Bajandas. New York: Plenum Press, pp. 145-178.

—— and BERTHOZ, A. (1975) Is the prepositus hypoglossi nucleus the source of another vestibular ocular pathway? *Brain Research, Amsterdam,* **86,** 121-127.

—— and HIGHSTEIN, S. M. (1975) Physiological identification of interneurons and motoneurons in the abducens nucleus. *Brain Research, Amsterdam,* **91,** 292-298.

BRANDT, TH., DICHGANS, J. and BÜCHELE, W. (1974) Motion habituation: inverted self-motion perception and optokinetic after-nystagmus. *Experimental Brain Research,* **21,** 337-352.

BUETTNER, U. W., BÜTTNER, U. and HENN, V. (1978) Transfer characteristics of neurons in vestibular nuclei of the alert monkey. *Journal of Neurophysiology,* **41,** 1614-1628.

BÜTTNER, U., BÜTTNER-ENNEVER, J. A. and HENN, V. (1977) Vertical eye movement related unit activity in the rostral mesencephalic reticular formation of the alert monkey. *Brain Research, Amsterdam,* **130,** 239-252.

COLLEWIJN, H. (1976) Impairment of optokinetic (after-) nystagmus by labyrinthectomy in the rabbit. *Experimental Neurology,* **52,** 146-156.

—— and VAN DER MARK, F. (1972) Ocular stability in variable visual feedback conditions in the rabbit. *Brain Research, Amsterdam,* **36,** 47-57.

—— WINTERSON, B. J. and DUBOIS, M. F. W. (1978) Optokinetic eye movements in albino rabbits: inversion in anterior visual field. *Science,* **199,** 1351-1353.

DAVIS-KING, W. M. and FUCHS, A. F. (1973) Brainstem neurons associated with vertical eye movements. *Neuroscience Abstracts,* p. 126, Society for Neuroscience, Bethesda.

—— LISBERGER, S. G., FUCHS, A. F. and EVINGER, L. C. (1974) Activity of simian mlf fibers related to eye movement and adequate vestibular stimulation. *Neuroscience Abstracts,* p. 185, Society for Neuroscience, Bethesda.

DELGADO-GARCIA, J., BAKER, R. and HIGHSTEIN, S. M. (1977) The activity of internuclear neurons identified within the abducens nucleus of the alert cat. In: *Control of Gaze by Brain Stem Neurons.* Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier, pp. 291-300.

DICHGANS, J., SCHMIDT, C. L. and GRAF, W. (1973) Visual input improves the speedometer function of the vestibular nuclei in the goldfish. *Experimental Brain Research,* **18,** 319-322.

EVINGER, L. C., FUCHS, A. F. and BAKER, R. (1977) Bilateral lesions of the medial longitudinal fasciculus in monkeys: Effects on the horizontal and vertical components of voluntary and vestibular induced eye movements. *Experimental Brain Research,* **28,** 1-20.

GERRITS, H. J. M. and VENDRIK, A. J. H. (1974) The influence of stimulus movements on perception in parafoveal stabilized vision. *Vision Research,* **14,** 175-180.

GRAYBIEL, A. M. and HARTWIEG, E. A. (1974) Some afferent connections of the oculomotor complex in the cat: an experimental study with tracer techniques. *Brain Research, Amsterdam,* **81,** 543-551.

HENN, V. and YOUNG, L. R. (1975) Ernst Mach on the vestibular organ 100 years ago. *Journal of Otolaryngology, Basel,* **37,** 138-148.

—— —— and FINLEY, C. (1974) Vestibular nucleus units in alert monkeys are also influenced by moving visual fields. *Brain Research, Amsterdam,* **71,** 144-149.

KING, W. M. and FUCHS, A. F. (1977) Neuronal activity in the mesencephalon related to vertical eye movements. In: *Control of Gaze by Brain Stem Neurons.* Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier, pp. 319-326.

—— Lisberger, S. G. and Fuchs, A. F. (1976) Responses of fibers in medial longitudinal fasciculus (mlf) of alert monkeys during horizontal and vertical conjugate eye movements evoked by vestibular or visual stimuli. *Journal of Neurophysiology*, **39**, 1135–1149.

Lennerstrand, G. (1975) Motor units in eye muscles. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Edited by G. Lennerstrand and P. Bach-y-Rita. Oxford: Pergamon Press, pp. 119–143.

Lisberger, S. G. and Fuchs, A. F. (1974) Response of flocculus Purkinje cells to adequate vestibular stimulation in alert monkey; fixation vs. compensatory eye movements. *Brain Research, Amsterdam*, **69**, 347–353.

—— —— (1978*a*) Role of primate flocculus during rapid behavioral modification of vestibuloocular reflex. I. Purkinje cell activity during visually guided horizontal smooth-pursuit eye movements and passive head rotation. *Journal of Neurophysiology*, **41**, 733–763.

—— —— (1978*b*) Role of primate flocculus during rapid behavioral modification of vestibuloocular reflex. II. Mossy fiber firing patterns during horizontal head rotation and eye movement. *Journal of Neurophysiology*, **41**, 764–777.

Lorente de Nó, R. (1933) Vestibulo-ocular reflex arc. *Archives of Neurology and Psychiatry, Chicago*, **30**, 245–291.

Miles, F. A. and Fuller, J. H. (1975) Visual tracking and the primate flocculus. *Science*, **189**, 1000–1002.

Pola, J. and Robinson, D. A. (1974) Mlf fiber activity in monkey during visually elicited and vestibular eye movement. *Neuroscience Abstracts*, p. 377, Society for Neuroscience, Bethesda.

—— —— (1978) Oculomotor signals in the medial longitudinal fasciculus of the monkey. *Journal of Neurophysiology*, **41**, 245–259.

Robinson, D. A. (1976) Adaptive gain control of vestibuloocular reflex by the cerebellum. *Journal of Neurophysiology*, **39**, 954–969.

—— (1977*a*) Linear addition of optokinetic and vestibular signals in the vestibular nucleus. *Experimental Brain Research*, **30**, 447–450.

—— (1977*b*) Vestibular and optokinetic symbiosis: an example of explaining by modelling. In: *Control of Gaze by Brain Stem Interneurons*. Edited by A. Berthoz and R. Baker. Amsterdam: Elsevier, pp. 49–58.

—— (1978) The functional behavior of the peripheral oculomotor apparatus: a review. In: *Disorders of Ocular Motility*. Edited by G. Kommerell. München: Bergmann Verlag, pp. 43–61.

Skavenski, A. A., Robinson, D. A., Steinman, R. M. and Timberlake, G. T. (1975) Miniature eye movements of fixation in rhesus monkey. *Vision Research*, **15**, 1269–1273.

Steinman, R. M., Haddad, G. M., Skavenski, A. A. and Wyman, D. (1973) Miniature eye movement. *Science*, **181**, 810–819.

Uemura, T. and Cohen, B. (1972) Vestibulo-ocular reflexes: effects of vestibular nuclear lesions. In: *Basic Aspects of Central Vestibular Mechanisms*. Edited by A. Brodal and O. Pompeiano. Amsterdam: Elsevier, pp. 515–528.

Waespe, W. and Henn, V. (1977) Neuronal activity in the vestibular nuclei of the alert monkey during vestibular and optokinetic stimulation. *Experimental Brain Research*, **27**, 523–538.

Winterson, B. J. and Collewijn, H. (1976) Microsaccades during finely guided visuomotor tasks. *Vision Research*, **16**, 1387–1390.

—— and Robinson, D. A. (1975) Fixation by the alert but solitary cat. *Vision Research*, **15**, 1349–1352.

Zee, D. S., Yee, R. D. and Robinson, D. A. (1976) Optokinetic responses in labyrinthine-defective human beings. *Brain Research*, **113**, 423–428.

Divided Consciousness. Multiple Controls in Human Thought and Action. By Ernest R. Hilgard. 1977. Pp. 318. Chichester and New York: John Wiley. Price £12·10.

This is not a book for the typical neurologist. It is not, in fact, a book for the typical anyone. But it is a book that ought to be of interest to a broad range of readers, both inside and outside the neurosciences, at least to those readers with broad interests. Donald Hebb is quoted on the jacket as describing it as '. . . the most important current development in psychology with a potential significance for an understanding of the mind that is hard to overestimate'. Perhaps it is not all that hard, but it would be very easy and dangerous to underestimate.

Professor Hilgard's book is literally about divided consciousness, as evidenced in hypnosis, fugue states, amnesia, and automatic writing. Interest in these phenomena is, of course, not new (and Hilgard gives us delightful historical examples of just how important they were to our scientific forebears—for instance, William James sitting outside F. W. H. Myers' hospital room when Myers was dying in the hope of catching a message when Myers' spiritual self departed his earthly body. 'James', says Hilgard, 'was disappointed'). There has long been a plethora of anecdotal or cosmological texts on these subjects. There are two quite new features in Hilgard's book. The first is its experimental approach. It will come as a genuine surprise to many readers to see how careful, painstaking and systematic are the laboratory studies that Hilgard and his colleagues at Stanford have carried out on hypnosis and automatic writing. They offer not only psychometric predictors of 'the hypnotizable person', obviously based on much empirical work, but more importantly they have examined in a quite matter-of-fact way questions such as the validity of age regression in hypnosis, whether there is interference between tasks induced by post-hypnotic suggestion and concurrent tasks, the extent to which pain and other sensory thresholds can be altered by hypnosis, the completeness and character (sometimes divided) of post-hypnotic amnesia, and a host of related questions. They are as objective in tone and approach regarding these matters as if they were dissecting a frog (well, almost).

The second feature of the book is its serious attempt to relate issues of divided consciousness to contemporary and sophisticated developments in human experimental psychology. It will come as no surprise to two generations of psychologists who were nurtured as students on Hilgard's highly informative, authoritative and eminently readable textbooks of learning and experimental psychology to see his effort here to integrate issues across a broad spectrum. While not going into the questions at any great depth, he points to the connections between hypnotic and amnesic phenomena and theories of attention as developed by Deutsch, Norman and Treisman, including the evidence from dichotic listening. He points us to some of the relevant modern analyses of memory, such as Bower (with whom, in fact, he wrote his fourth edition of his classic *Theories of Learning*), Baddeley, Atkinson and others. He is also concerned about the nature of control mechanisms, both the executive and monitoring aspects, and refers us to Newell and Simon and to Neisser. He is aware of some of the relevant facts of the experimental evidence as well as clinical details of amnesia, and of the evidence from commissurotomized patients. These connections are often made briefly in 'Notes' at the end of each chapter and serve perhaps more as signposts to a rich and broad horizon than as a detailed atlas.

Hilgard discusses his subject-matter in the theoretical context of 'dissociation'. If we substitute 'disconnection', we might see the relevance to neurology; and the discussion of 'hierarchical control mechanisms' can find roots in Jackson and Kenneth Craik. The author emerges less as a prophet than as a sober, tolerant and transparently honest enquirer who, with his wife and other colleagues, has offered painstaking and useful laboratory methodologies and findings about phenomena which have tended to be treated as bizarre and suspect, but which are here convincingly related to concepts of central importance both to psychology and neurology.

L. WEISKRANTZ

Advances in Neurochemistry. Vol. 3. Edited by B. W. Agranoff and M. H. Aprison. 1978. Pp. 304. New York: Plenum. Price £20·47.

This series continues to fulfil the initial purpose of providing specialized reviews on neurochemistry. A good example is provided in the first chapter which is entitled '2′, 3′ cyclic nucleotide phosphodiesterase (CNPase)'. Although myelin is largely devoid of enzyme activity, CNPase is concentrated within the membrane. Estimation of the enzyme activity serves as an index of myelin. Thus more CNPase activity is found in oligodendrocytes than other cells and the enzyme is found in myelin-like material associated with myelination. The properties of this unusual enzyme are described and there is an account of its use as a membrane marker. Another modern technique for identifying specific antigens in tissue sections is that of immunohistochemistry. In the second chapter there is a comprehensive account of the use of the method in identifying and localizing enzymes (for example, choline acetyltransferase or glutamate decarboxylases) and protein antigens (for example, myelin basic protein, the S-100 protein). For instance, using the immunoperoxidase technique glial fibrillary protein can be localized within astrocytes or in brain tumour tissue. Currently available methods for the isolation and characterization of synaptic structures is reviewed in Chapter 3. Subcellular fractionation results in the isolation of synaptosomes which have some of the properties of intact cells and from these particles synaptic membranes can be separated. Synaptosomes also serve as a source of synaptic vesicles and mitochondria. Synaptic functional complexes containing pre- and post-synaptic membranes can be usefully isolated and their chemistry studied.

In Chapter 4 the multiple roles of glutamate and aspartate are reviewed. These amino acids are important constituents of brain proteins but the dicarboxylic acids have a key role in energy and intermediary metabolism. Glutamate and aspartate are important excitatory amino acid transmitters both in the invertebrate and vertebrate nervous system. Within the CNS glutamate and GABA are probably compartmentalized, GABA released from nerve terminals is converted to glutamine within glia and then recycled as glutamine to the neuron where glutamate is reformed.

The topic of the final chapter is biochemical aspects of transmission at inhibitory synapses. Much of the evidence centres on the inhibitory role of glycine in the spinal cord where this amino acid is concentrated. However, glycine is also found in the brain and retina. There are interesting findings of changes in glycine concentration in neurological disease (for example, in hyperglycinæmia syndrome and in spasticity).

A. N. DAVISON

Neurotransmitter Receptor Binding. Edited by H. I. Yamamura, S. J. Enna and M. J. Kuhar. 1978. Pp. 206. New York: Raven Press. Price $22.10.

It is only in the last ten years or so that binding of high specific activity ligands has been used for measuring neurotransmitter receptors. A good example is the development of α-bungarotoxin as a stable agent for binding to nicotinic cholinergic receptors. This has proved an invaluable tool for the isolation of the purified protein. Following the widespread use of labelled snake venom the same principles were quickly applied to hormone, peptide and neurotransmitter receptor binding. Although the methods used are relatively simple a great deal of care has to be taken in ensuring the specificity of binding. For instance ^{125}I-insulin binds with high affinity to talcum powder and stereospecific binding of opiates within the brain has been shown to be with cerebroside of the white matter. Subsequently the significant observation was made that opiates bind with high affinity stereospecifically to brain membranes. This underlines the importance of a detailed and rigorous demonstration of specificity of receptor interactions in the same tissue.

This short book is therefore valuable because it deals with fundamental principles and procedures. It does not include a comprehensive review of the enormous amount of data on receptors presently available but is rather a laboratory guide to practical problems. Thus there are chapters on model systems, criteria for receptor identification and binding study methodology. The biochemistry of receptors (for example, purification and immunochemistry), and histochemical localization are discussed. Novel uses of receptors are referred to in the last three chapters which are on assay of drugs and neurotransmitters, on drug screening and disease.

A. N. DAVISON

Advances in Prostaglandin and Thromboxane Research. Vol. 3. Edited by C. Galli, G. Galli and G. Porcellati. 1978. Pp. 218. New York: Raven Press. Price $28.60.

Advances in Prostaglandin and Thromboxane Research. Vol. 4. Edited by F. Coceani and P. M. Olley. 1978. Pp. 427. New York: Raven Press. Price $45.50.

Advances in Prostaglandin and Thromboxane Research. Vol. 5. Edited by J. C. Frolich. 1978. Pp. 246. New York: Raven Press. Price $31.20.

The publication of three further volumes in this series all within one year (1978) is in itself testimony to the importance of this rapidly expanding area of biochemical research. The literature on prostaglandins is enormous and there are already two journals devoted exclusively to them. Against this background *Advances in Prostaglandin and Thromboxane Research* will be welcomed by workers actively engaged in research as well as those merely interested in attempting to keep up to date with the latest developments.

Perhaps it is in relation to the nervous system that least is currently known concerning the biological significance of this important group of polyunsaturated fatty acids and their precursors, though a number of groups are now actively engaged in this field. Certainly there is much useful information in these volumes for both clinical neurologists and neurochemists.

Volume 3 is mainly concerned with phospholipases and their relation to prostaglandin and endoperoxide synthesis in a variety of tissues and cell types including nerve and platelets. This is timely in view of recent trends in thinking which attach greater functional importance to the endoperoxides, thromboxanes and prostacyclins than to the prostaglandins themselves. As far as the brain is concerned although the normal prostaglandin content is low and the synthetic capacity for prostaglandins high it is the liberation of the endogenous fatty acid precursors, arachidonic acid and linoleic acid from phospholipids, which is the rate-limiting step and probably the one of greatest biological importance.

Very detailed studies have been carried out on platelets and one of the most interesting chapters deals with the calcium-dependent stimulation of thromboxane and prostaglandin biosynthesis by ionophores and this certainly has important implications for biosynthesis in the brain too. Also of probable importance in relation to future work on the central nervous system are the ideas expressed in the chapter dealing with stimulation of arachidonic acid release and prostaglandin synthesis by cyclic nucleotides in the cultured fibroblast model. The remainder of the volume comprises a balanced and reasonably comprehensive account of the distribution, properties and function of phospholipases. All the chapters are by authors actively engaged in current research.

Volume 4 entitled *Prostaglandins and Perinatal Medicine* comprises a multidisciplinary approach to an important topic, and at the same time updates much information concerning prostaglandins and thromboxanes presented in the first two volumes of the series.

There is an introductory section comprising two chapters which deals with current concepts of the prostaglandin system as a whole. The first by Samuelsson, Folco, Granstrom, Kindahl and Malmsten is concerned with the general biochemical and physiological background which is to be seen as important in such a ubiquitous group of compounds. The second by J. R. Vane reviews the metabolic pathway of arachidonic acid, stresses the biological importance of thromboxane and prostacyclin and gives a brief account of the inhibitors of the respective synthetic enzyme systems. A later section deals specifically with the role of prostaglandins on the fœtus, uterus, placenta and ductus arteriosus; and there is a further chapter on the action of prostaglandins on organogenesis.

There is however, in addition, an important section devoted to the central nervous system. This comprises four chapters which deal successively with polyunsaturated fatty acids in relation to brain development, the relationship between the prostaglandin system and epileptogenesis, prostaglandins and central thermoregulation and finally the biosynthesis of prostaglandins and thromboxanes in the brain. This short section is a useful recent review and source of references for those interested in research into prostaglandins and the central nervous system.

Volume 5 is concerned with the methodology involved in prostaglandin research. This is an important review for the laboratory worker in a field where methodology is difficult and where methods have been suspect in the past. The author claims that sufficient detail is provided for accurate reproduction in any laboratory but it is questionable whether those already in the field would regard the data presented as in any way comprehensive even for the more commonly accepted methods. Nevertheless for those setting out in the field the volume will be a useful and balanced guide as to what can be expected from the various techniques available. Successive chapters deal with extraction and chromatographic procedures, gas-liquid chromatography with and without the additional facility of mass spectrometry, radioimmunoassay and bioassay. There is also a section on high-pressure liquid chromatography, though it is a pity that this recent and very important technique has not received more attention.

The series as a whole can be strongly recommended. Production is to a high standard, the diagrams are clear and well labelled, and the bibliography is adequate with most of the references up to 1975 but with a sprinkling as late as 1977.

P. T. LASCELLES

Treatment of Pituitary Adenomas. First European Workshop on Treatment of Pituitary Adenomas at Rottach-Egern. Edited by R. Fahlbusch and Klaus v. Werder. 1978. Pp. 445. Stuttgart: Georg Thieme. Price DM 78.00.

These are the proceedings, published in a soft cover but well printed and illustrated, of a meeting held in 1976. It contains papers on the diagnosis, both endocrinological and radiological, of pituitary tumours and their treatment by surgery and external irradiation or implantation. Much of its interest lies in its demonstration of how far the clinical diagnosis has shifted from neurological or ophthalmological to endocrinological. There is a predominance of papers on endocrinologically active adenomas, prolactin secreting and those producing acromegaly and Cushing's syndrome. Both diagnosis and the effects of treatment on hormonal function are considered in a number of papers.

The transphenoidal operation, kept alive by a few surgeons over the years after Cushing virtually abandoned it, is seen here to have usurped the subfrontal operation in the treatment of these tumours. There is only one paper on craniotomy for pituitary adenoma. The operating microscope, the image intensifier and the advocacy of Guiot, who here writes an excellent review of this type of surgery, and of Hardy, have brought about this remarkable change.

Although not free from the usual defects of published proceedings, this book contains much of interest to neurosurgeons.

T. T. KING

Taurine and Neurological Disorders. Edited by André Barbeau and Ryan J. Huxtable. 1978. Pp. 482. New York: Raven Press. Price $46.80.

Until recently little attention has been paid to the possible biological role of taurine even though it is present in high concentration in the brain, especially in early development. It is unusually stable metabolically, and as indicated in this book it is not metabolized to iseothionate by mammalian tissue. Much of our taurine is derived from meat. Apart from bile acid synthesis regulation of taurine levels is through the kidney but it can be synthesized from cysteine. Carnivores may easily become deficient on a taurine-depleted diet, and quickly develop retinal changes. There is evidence that in the CNS, like some other amino acids, taurine acts as an inhibitory neurotransmitter or modulator. On release, taurine may be removed from the post-synaptic receptor site by a high affinity uptake mechanism. Besides a possible transmitter role it has also been suggested that taurine is involved in membrane stabilization and in movement of calcium ion, a process of particular importance to the heart.

In this book, which updates a previous volume on the subject, a number of experts review data on all aspects of the biology of taurine and deal with some of the fascinating implications for the neurologist. For example it has been found that Friedrich's ataxia is associated with increased taurine excretion, and there is an important indication that imbalance in taurine relates to changes in glutamate and GABA concentration in the epileptic brain. As a result taurine has been used in the treatment of experimental and human epilepsy but so far with little success in man. Since this book contains new basic data as well as considerable new ideas about the possible function and role of taurine in neurological disease, it should be of value to both basic scientists and research-minded clinicians.

A. N. DAVISON

Chronic Progressive External Ophthalmoplegia. By L. A. K. BASTIAENSEN. 1978. Pp. 383. Leyden: Stafleu's Scientific Publishing Company. Price not stated.

This thesis consists largely of a review of the literature, up to 1977, concerning clinical and pathological features of the various disorders comprising the syndrome of chronic progressive external ophthalmoplegia, with and without other features. There is a strong historical bias throughout the book. Particular emphasis is placed on ocular myopathies and oculopharyngeal muscular dystrophy but other rare disorders are considered in some detail, in relation to the author's experience. Introductory chapters briefly consider the structure and function of muscle fibres in the external ocular muscles but biochemical aspects of the disorders discussed receive relatively little attention. Few new conclusions emerge but the work is a useful source of information.

MICHAEL SWASH

Nerves and Nerve Injuries. By Sir SYDNEY SUNDERLAND. Second Edition. 1978. Pp. 1046. Edinburgh: Churchill Livingstone. Price £55·00.

The second edition of Sir Sidney Sunderland's *Nerves and Nerve Injuries* appears ten years after the first. Sir Sydney tells us that this new edition contains more than 3000 new references, though he goes on to lament, 'much of what has been reported in the literature is repetitious and irrelevant largely because of an astonishing ignorance of information that is readily available', a true *cri de cœur.* He reaffirms that his central objective has been to bring all aspects of the complicated subject of nerve injury and nerve repair together in an orderly and meaningful way.

Nerves and Nerve Injuries has provided an authoritative source for medical and surgical neurologists for the past decade. The new edition contains many rewritten chapters and much new material. It is an important work of reference which should be found in all departmental libraries. The price is not excessive for a large, well-produced, comprehensive work.

R. A. HENSON

Reviews of Neuroscience. Vol. 3. Edited by S. Ehrenpreis and I. J. Kopin. 1978. Pp. 238. New York: Raven Press. Price $25.35.

A new volume in this attractive, well-presented series. A new challenge for the reviewer trying to synthesize impressions of six chapters on widely different topics. Perhaps the first three chapters can be considered together inasmuch as they all derive from the implications of one principle—neurobiological frugality. Thus, each transmitter can interact with other transmitters in different ways and perform different tasks. Different transmitters are made, released and destroyed by enzymic machines which though separated spatially are of biochemically overlapping specificities. This economy in the use of materials leads to a tremendous apparent complexity of design. Most organs might have been made by the calm Pantocrator shown on Byzantine apses but it begins to seem as if the brain was made by a manic toymaker whose over-ingenuity makes investigation a daunting task. Did he who made the lung make thee?

In the first of these three chapters, Erikson gives an account of a rapidly growing and at present confusing field—how different transmitter systems interact as suggested by evidence from drug experiments and brain disease. Kuhar and Atweh very clearly summarize how transmitter-containing tracts are distributed in the brain and Raiteri and Levi deal with mechanisms of release of 5-HT and catecholamines from synaptosomes. These chapters and the one by Mandel and Pasankes-Morales on taurine in the nervous system should interest neurobiologists in general. The status of taurine is, however, still in doubt though it has a number of properties consistent with a transmitter role.

The remaining chapters are probably of more use to prospective specialists in the fields they describe. Fieve discusses the use of lithium in affective disorders from a clinical point of view but with little space given to the large, albeit inconclusive, literature on its mode of action. Finally, Nagatsu and Tsukuda review methods for the separation of different brain cell types.

G. CURZON

Non-invasive Measurement of Regional Cerebral Blood Flow in Man. Edited by V. D. Deshmukh and John Stirling Meyer. 1978. Pp. 222. New York and London: Spectrum. Price £14·00.

Regional Cerebral Blood Flow: Regulation, Measurement and Changes with Disease. By H. J. Gelmers. 1978. Pp. 96. Monographs on Clinical Neurology and Neurosurgery. Assen, Netherlands: Royal Vangorcum. Price Dfl. 60.00.

The first of these two monographs describes the background to non-invasive methods of study of the cerebral circulation, in particular the use of radioactive xenon inhalation method as modified in Baylor College of Medicine, Texas. Coming from the laboratory of Professor John Stirling Meyer, it is, as might be expected, a wide ranging and informative little book. The basic anatomy of the cerebral circulation is described briefly, but in adequate detail, and the main features of the various techniques of regional cerebral blood flow estimation, the intra-arterial, intravenous and inhalational methods, are described. There is a useful chapter on the handling of radioactive gases by the physicists involved in the laboratory, and a detailed description of the system in current use in Baylor, not unrepresentative of the average inhalational system in use throughout the world. The broad field of cerebrovascular physiology and pharmacology is briefly but somewhat uncritically covered, but here as in the rest of the book, an excellent coverage of literature is appended and the student is free to make his own analysis by wider reading if he wishes. It is in the clinical application of techniques of regional blood flow that an otherwise commendable little book falters somewhat, since here the many problems inherent in blood flow analysis in pathological tissue are scarcely touched upon, rather strangely one might have thought, when Ravens' work on the microvasculature received an annotation in the anatomical section, although its implications, particularly on compartmental transferance in pathological states seems largely to have been missed. Nevertheless, the current state of investigation in a wide variety of clinical subjects is annotated, and the monograph as a whole can be recommended as an effective coverage of the state of the art at the present time.

H. J. Gelmer's little book collects the experience of one clinic in clinical cerebral blood flow measurements. It includes a relatively brief but uncontroversial chapter on the physiology of the cerebral circulation, and another on the standard methods of technique. An assessment of published literature on the clinical use of cerebral blood flow, and a chapter on the use made in the particular clinic in question are also included together with a detailed description of the current method of inhalational cerebral blood flow methods which the author uses. This chapter is probably the most valuable in the book.

The author presents an optimistic view of the clinical utility of cerebral blood flow analysis, which is scarcely borne out by the analysis of his own material; in particular, the utility of cerebral blood flow measurements in the assessment of shunts as in arteriovenous malformations, has yet to be determined. Any circumstance in which the saturation elution upon which the method relies, is so clearly disturbed, carries grave questions in analysis.

The book has some 96 pages including references, and is therefore quick to read, but it suffers from numerous minor and irritating errors in proof reading, contains no information which is not available elsewhere, often already in monograph form, and at the equivalent of about £15·00 can scarcely be recommended as value for money.

LINDSAY SYMON

Molecular Neurobiology of the Mammalian Brain. Edited by P. L. McGeer, J. C. Eccles and E. G. McGeer. 1978. Pp. 644. New York and London: Plenum Press. Price £23·62.

This excellent book can be recommended not only to neurobiology students but also to neuroscientists and clinicians. Though not primarily written for the specialist, it provides an authoritative, up-to-date integrated account of the anatomy, physiology and biochemistry of the nervous system in relation to its function which all will find valuable. Moreover, the authors write in a clear readable style and the text is amply illustrated with attractive diagrams.

The book is divided into three parts. The first deals with the architecture and operation of the nervous system. There are short sections on morphology of the mammalian brain, neurophysiology and synaptic transmission within peripheral and central nervous system. Besides providing a comprehensive summary of current views on the mechanism of synaptic transmissions, the authors include their own commentary on the role of individual nerve cells and some of their simplest organizations. Following Dale's hypothesis it is still generally agreed that each neuron manufactures and stores a single chemical transmitter. This becomes its biochemical fingerprint and principal method of inter-neuronal communication. It is pointed out that a lot is known about the anatomical connections and physiological functions of neurons but rather less about their individual neurotransmitters. As indicated in Part II acetylcholine is the best established transmitter. Its nicotinic action is mediated on the receptor by an *ionotropic* mechanism because its principal function is to open ionic paths across the post synaptic membrane. Other likely transmitters—glycine in the spinal cord and importantly GABA in the CNS—work by this rapid action with accompanying large changes in conductance. There is another mechanism of neurotransmission which involves a second messenger in the post-synaptic cell. This *metabotropic* system is typified by dopamine which operates via cyclic AMP and produces short-term alterations in membrane potential and longer-term trophic and plastic changes related to neural membrane conformation. Quantitatively glutamate and GABA-mediated neurons dominate the central nervous system but the possibility that certain peptides (for example, carnosine, enkephalin) and other miscellaneous compounds (for example, taurine, purines) may act as transmitters or neuromodulators is also discussed.

The integrative aspects of brain function are reviewed in the final part of the book. Brain structural development and plasticity is discussed. There are excellent chapters on the integrated control by the brain of movement through the musculoskeletal system and on the superimposed basic behavioural patterns. The action of psychoactive drugs is summarized. The final chapters are on neuronal mechanisms (largely excluding biochemistry) involved in learning and memory, and perception, speech and consciousness.

Despite the considerable amount of information contained in this book the authors are quite aware that 'we are only at the beginning of our understanding of signaling in the nervous system'.

A. N. DAVISON

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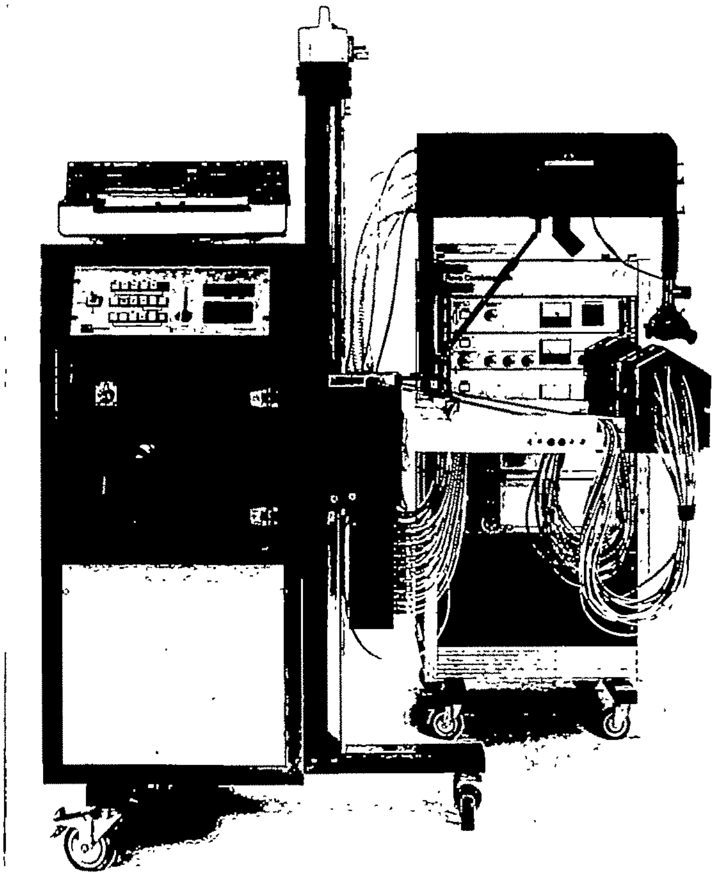

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MAPPING OF LOCAL CEREBRAL FUNCTIONAL ACTIVITY BY MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION WITH [^{14}C]DEOXYGLUCOSE[1]

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INTRODUCTION

THE brain is a complex organ composed of many structural and functional components with markedly different and independently regulated levels of functional and metabolic activity. In more homogeneous organs that do readily recognizable physical work, such as heart, skeletal muscle, kidney, etc., a close relationship between functional activity and energy metabolism is well established. The existence of a similar relationship in the tissues of the central nervous system has been more difficult to prove, partly because of uncertainty about the nature of the work associated with nervous functional activity, and, more importantly, because of difficulty in assessing the levels of functional and metabolic activities in the same functional component of the brain at the same time. Pathological and pharmacological conditions with gross and diffuse effects on cerebral functional activity, particularly alterations in the level of consciousness, have been shown to be associated with changes in metabolic rate in the brain as a whole (Kety, 1950, 1957; Lassen, 1959; Sokoloff, 1976), but such associations could just as readily be explained by independent consequences of cellular dysfunction as by a direct relationship between cerebral functional activity and energy metabolism. Changes in cerebral metabolic rate have generally not been found during physiological alterations of cerebral functional activity (Lassen, 1959; Sokoloff, 1969, 1976). What has clearly been needed is a method to measure the rates of energy metabolism in specific discrete regions of the brain in different states of functional activity. The recently developed [^{14}C]deoxyglucose method (Sokoloff, Reivich, Kennedy, Des Rosiers, Patlak, Pettigrew, Sakurada and Shinohara, 1977) appears to fulfil this need, and it has been used to demonstrate a close relationship between functional activity and energy metabolism in structural and functional components of the central nervous system (Sokoloff, 1975; Kennedy, Des Rosiers, Jehle, Reivich, Sharp and Sokoloff, 1975; Kennedy, Des Rosiers, Sakurada, Shinohara, Reivich, Jehle and Sokoloff, 1976; Sokoloff, 1977).

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[1] Based on an Invited Lecture delivered at the Scientific Meeting which was held on April 5, 1978, to celebrate the Centenary of *Brain*.

METHODS

Background

The application of quantitative autoradiographic techniques for the measurement of local tissue concentrations of chemically inert, radioactive, diffusible tracers has made it possible to determine the rates of blood flow simultaneously in most of the individual structural and functional components of the brain (Landau, Freygang, Rowland, Sokoloff and Kety, 1955; Reivich, Jehle, Sokoloff and Kety, 1969). The extension of quantitative autoradiography to the determination of local cerebral metabolic rate with the same degree of anatomical resolution has proved to be more difficult because of the inherently greater theoretical complexity of the problem and the unsuitability of the radioactive species of the usual substrates of cerebral energy metabolism, oxygen and glucose. The radioisotopes of oxygen have too short a physical half-life, and the labelled products of the metabolism of both oxygen and glucose have too short a biological half-life in the cerebral tissue. We have, therefore, employed 2-[^{14}C]deoxyglucose, an analogue of glucose with special properties that make it particularly appropriate to trace glucose metabolism and to measure the rates of local glucose consumption within the various functional and structural components of the brain. Like the local cerebral blood flow techniques, the method is applicable to conscious as well as anæsthetized laboratory animals.

Theory

2-Deoxy-D-glucose (DG) is transported from blood to brain by the same carrier that transports glucose, and like glucose it is phosphorylated in the cerebral tissues by hexokinase. Deoxyglucose and glucose are, therefore, competitive substrates for both transport and hexokinase-catalysed phosphorylation. Unlike glucose-6-phosphate (G-6-P), however, which is rapidly metabolized further to CO_2 and H_2O, 2-deoxyglucose-6-phosphate (DG-6-P) cannot be converted to fructose-6-phosphate by phosphohexoseisomerase and is, therefore, essentially trapped in the tissues, at least for the intervals of time that concern us. We have determined the half-lives of [^{14}C]DG-6-P in various cerebral tissues and found none shorter than six hours (Sokoloff *et al.*, 1977). When [^{14}C]DG is introduced into the circulation, the amount of [^{14}C]DG-6-P accumulated in any cerebral tissue at any time later equals the integral of the rate of [^{14}C]DG phosphorylation with respect to time in that tissue, and this quantity is in turn quantitatively related to the amount of glucose that has been phosphorylated over the same time period, depending on the time course of the relative concentrations of [^{14}C]DG and glucose in the precursor pools and the kinetic constants for hexokinase with respect to both DG and glucose. With cerebral glucose utilization in a steady state, the amount of glucose phosphorylated during the interval of time equals the steady state flux of glucose through the hexokinase-catalysed step times the duration of the interval, and the net of flux of glucose through this step equals the rate of glucose utilization.

It is beyond the scope of this report to present the details of the model and the theoretical analyses which form the basis of this method. These are presented elsewhere (Sokoloff *et al.*, 1977). Briefly, the basic principles are as follows: the model assumes a steady state for glucose (that is, constant plasma glucose concentration and constant rates of tissue glucose consumption) throughout the period of the procedure; homogeneous tissue compartments within which the precursor concentrations of [^{14}C]DG and glucose are uniform and exchange directly with the plasma; and tracer concentrations of

[^{14}C]DG (i.e. molecular concentrations of free [^{14}C]DG essentially equal to zero). Mathematical analysis of the model leads to the following equation:

$$R_i = \frac{C_i^*(T) - k_1^* \exp\{-(k_2^* + k_3^*)T\} \int_0^T C_P^* \exp\{(k_2^* + k_3^*)t\}\, dt}{\left[\frac{\lambda V_m^* K_m}{\Phi V_m K_m^*}\right]\left[\int_0^T (C_P^*/C_P)\, dt - \exp\{-(k_2^* + k_3^*)T\} \int_0^T (C_P^*/C_P) \exp\{(k_2^* + k_3^*)t\}\, dt\right]}$$

where R_i equals the calculated rate of glucose utilization per gramme of tissue, i; T equals time of killing, $C_i^*(T)$ equals the total concentration of [^{14}C]DG and [^{14}C]DG-6-P in issue, i, at time, T, determined by quantitative autoradiography; C_P^* and C_P equal the arterial plasma concentrations of [^{14}C]DG and glucose, respectively; k_1^*, k_2^* and k_3^* are the rate constants for the transport of [^{14}C]DG from the plasma to the tissue precursor pool, for its transport back from tissue to plasma, and for the phosphorylation of free [^{14}C]DG in the tissue, respectively; λ equals the ratio of the distribution space of [^{14}C]DG in the tissue to that of glucose; Φ equals the fraction of glucose which once phosphorylated continues down the glycolytic pathway; and K_m^* and V_{max}^* and K_m and V_{max} are the familiar Michaelis-Menten kinetic constants of hexokinase for [^{14}C]DG and glucose, respectively.

The rate constants are determined in a separate group of animals by a non-linear, iterative, computer-routine which provides the best-fit of the experimentally determined time courses of tissue and plasma [^{14}C] concentrations to an equation which defines the time course of tissue concentration in terms of the time, the history of the plasma concentration, and the rate constants (Sokoloff *et al.*, 1977). The λ, Φ and the enzyme kinetic constants are grouped together to constitute a single, lumped constant (*see equation*). It can be shown mathematically that this lumped constant is equal to the asymptotic value of the product of the ratio of the cerebral extraction ratios of [^{14}C]DG and glucose and the ratio of the arterial blood to plasma specific activities when the arterial plasma [^{14}C]DG concentration is maintained constant. The lumped constant is also determined in a separate group of animals from arterial and cerebral venous blood samples drawn during a programmed intravenous infusion which produces and maintains a constant arterial plasma [^{14}C]DG concentration (Sokoloff *et al.*, 1977). These essential constants have thus far been determined only in the albino rat and Rhesus monkey, and local cerebral glucose utilization (LCGU) has been quantitatively determined in these species in a variety of functional states.

Procedure

The procedure is to inject a pulse of [^{14}C]DG intravenously at zero time and to decapitate the animal at a measured time, T, 30–45 minutes later; in the interval timed arterial samples are taken for the measurement of the time courses of the plasma [^{14}C]DG and glucose concentrations. Tissue ^{14}C concentrations are measured at time, T, by the quantitative autoradiographic technique (Reivich *et al.*, 1969; Sokoloff *et al.*, 1977). The total rates of glucose utilization are calculated from these measured variables by means of the operational equation.

RATES OF LOCAL CEREBRAL GLUCOSE UTILIZATION IN THE RAT AND MONKEY

The rates of local cerebral glucose utilization have been measured in the normal conscious and anæsthetized albino rat and in the conscious Rhesus monkey. The rates in the conscious rat vary widely throughout the brain with the values in white matter distributed in a narrow low range and the values in grey structures broadly distributed around an average which is about three times greater than that of white matter (Table 1). The highest values are in structures of the auditory system with the inferior colliculus clearly the most metabolically active structure in the brain (Table 1).

TABLE 1. REPRESENTATIVE VALUES FOR LOCAL CEREBRAL GLUCOSE UTILIZATION IN THE NORMAL CONSCIOUS ALBINO RAT AND MONKEY [μmol/100 g/min)

Structure	*Albino rat** (*n* = *10*)	*Monkey*† (*n* = *7*)
Grey matter		
Visual cortex	107 ± 6	59 ± 2
Auditory cortex	162 ± 5	79 ± 4
Parietal cortex	112 ± 5	47 ± 4
Sensorimotor cortex	120 ± 5	44 ± 3
Thalamus: lateral nucleus	116 ± 5	54 ± 2
Thalamus: ventral nucleus	109 ± 5	43 ± 2
Medial geniculate body	131 ± 5	65 ± 3
Lateral geniculate body	96 ± 5	39 ± 1
Hypothalamus	54 ± 2	25 ± 1
Mamillary body	121 ± 5	57 ± 3
Hippocampus	79 ± 3	39 ± 2
Amygdala	52 ± 2	25 ± 2
Caudate-putamen	110 ± 4	52 ± 3
Nucleus accumbens	82 ± 3	36 ± 2
Globus pallidus	58 ± 2	26 ± 2
Substantia nigra	58 ± 3	29 ± 2
Vestibular nucleus	128 ± 5	66 ± 3
Cochlear nucleus	113 ± 7	51 ± 3
Superior olivary nucleus	133 ± 7	63 ± 4
Inferior colliculus	197 ± 10	103 ± 6
Superior colliculus	95 ± 5	55 ± 4
Pontine grey matter	62 ± 3	28 ± 1
Cerebellar cortex	57 ± 2	31 ± 2
Cerebellar nuclei	100 ± 4	45 ± 2
White matter		
Corpus callosum	40 ± 2	11 ± 1
Internal capsule	33 ± 2	13 ± 1
Cerebellar white matter	37 ± 2	12 ± 1

The values are the means ± standard errors from measurements made in the number of animals indicated (n). * From Sokoloff *et al.* (1977). † From Kennedy, Sakurada, Shinohara, Jehle and Sokoloff (1978).

The rates of local cerebral utilization in the conscious monkey exhibit similar heterogeneity, but they are generally one-third to one-half of the values in corresponding structures of the rat brain (Table 1). The differences in rates in the rat and monkey brain are consistent with the different cellular packing densities in the brains of these two species.

There are no comparable values for comparison, but the values in the rat appear to be close to those to be expected from the average metabolic rates determined by

Eklöf, Lassen, Nilsson, Norberg and Siesjö (1973) in the rat cerebral cortex and by Nilsson and Siesjö (1976) in the rat brain as a whole. Similarly, the values of the monkey agree closely with those to be expected from the average values obtained by Schmidt, Kety and Pennes (1945) in the brain as a whole of the lightly anæsthetized monkey.

EFFECTS OF ANÆSTHESIA

General anæsthesia induced by thiopental reduces the rates of glucose utilization in all structures of the rat brain (Table 2). The effects are not uniform, however. The greatest reductions occur in the grey structures, particularly those of the primary sensory pathways. The effects in white matter, though definitely present, are relatively small compared with those in grey matter.

Table 2. Effects of Thiopental Anæsthesia on Local Cerebral Glucose Utilization in the Albino Rat*§

	Local cerebral glucose utilization (μmol/100 g/min)		
Structure	*Control (6)*†	*Anæsthetized (8)*†	*% effect*
Grey matter			
Visual cortex	111±5	64±3	−42
Auditory cortex	157±5	81±3	−48
Parietal cortex	107±3	65±2	−39
Sensorimotor cortex	118±3	67±2	−43
Lateral geniculate body	92±2	53±3	−42
Medial geniculate body	126±6	63±3	−50
Thalamus: lateral nucleus	108±3	58±2	−46
Thalamus: ventral nucleus	98±3	55±1	−44
Hypothalamus	63±3	43±2	−32
Caudate-putamen	111±4	72±3	−35
Hippocampus: Ammon's horn	79±1	56±1	−29
Amygdala	56±4	41±2	−27
Cochlear nucleus	124±7	79±5	−36
Lateral lemniscus	114±7	75±4	−34
Inferior colliculus	198±7	131±8	−34
Superior olivary nucleus	141±5	104±7	−26
Superior colliculus	99±3	59±3	−40
Vestibular nucleus	133±4	81±4	−39
Pontine grey matter	69±3	46±3	−33
Cerebellar cortex	66±2	44±2	−33
Cerebellar nucleus	106±4	75±4	−29
White matter			
Corpus callosum	42±2	30±2	−29
Genu of Corpus callosum	35±5	30±2	−14
Internal capsule	35±2	29±2	−17
Cerebellar white matter	38±2	29±2	−24

* Determined at 30 min following pulse of [^{14}C]deoxyglucose. † The values are the means ± standard errors obtained in the number of animals indicated in parentheses. All the differences are statistically significant at the $P < 0.05$ level. § From Sokoloff *et al.* (1977).

RELATIONSHIP BETWEEN LOCAL FUNCTIONAL ACTIVITY AND ENERGY METABOLISM

The results of a variety of applications of the method demonstrate a clear relationship between local cerebral functional activity and glucose utilization. The most striking demonstrations of the close coupling between function and energy metabolism are seen with experimentally induced local alterations in functional activity that are restricted to a few specific areas in the brain. The effects on local glucose consumption are then so pronounced that they are not only observed in

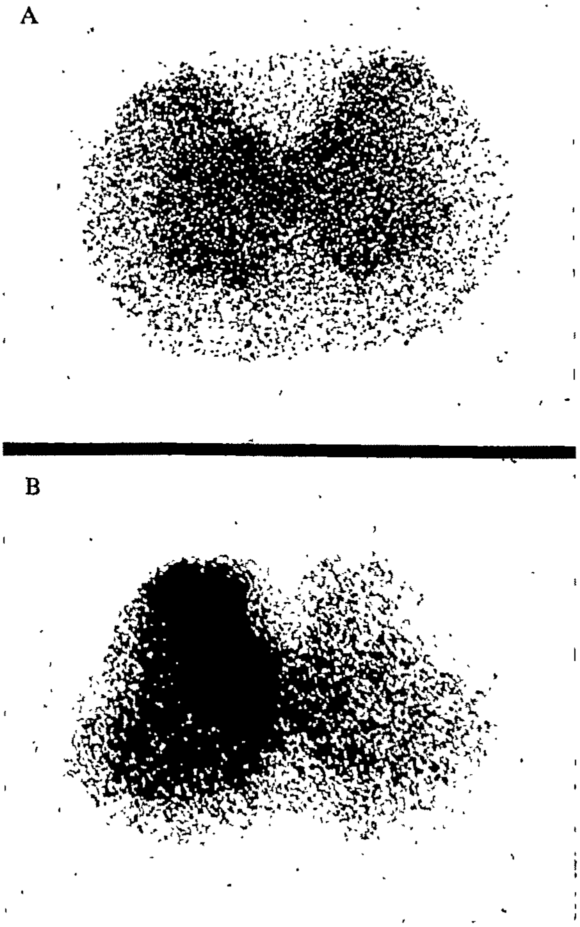

FIG. 1. Effects of increased functional activity in lumbar spinal cord produced by unilateral electrical stimulation of sciatic nerve on local tissue glucose utilization. A, autoradiograph of sections of lumbar spinal cord from control rat. B, autoradiograph of section of lumbar spinal cord from rat with unilateral electrical stimulation of sciatic nerve. Note bilateral symmetry of optical densities in control rat (A) and asymmetrical increase in optical density in dorsal horn ipsilateral to side of stimulation in animal with sciatic nerve stimulation (B). From Kennedy *et al.* (1975).

the quantitative results but can be visualized directly in the autoradiographs which are really pictorial representations of the relative rates of glucose utilization in the various structural components of the brain.

Effects of Increased Functional Activity: Electrical Stimulation

Fig. 1 illustrates the effects of increased neural activity resulting from electrical stimulation of the sciatic nerve in the rat under barbiturate anæsthesia. Such stimulation of one sciatic nerve causes pronounced increases in glucose consumption (that is, increased optical density in the autoradiographs) in the ipsilateral dorsal horn of the lumbar spinal cord (Kennedy *et al.*, 1975).

Effects of Experimental Focal Seizures

The local injection of 25 000 units of potassium benzyl penicillin into the hand-face area of the motor cortex of the Rhesus monkey has been shown to induce electrical discharges in the adjacent cortex and to result in recurrent focal seizures involving the face, arm and hand on the contralateral side (Caveness, 1969). Such seizure activity causes selective increases in glucose consumption in areas of motor cortex adjacent to the penicillin locus and in small discrete regions of the putamen, globus pallidus, caudate nucleus, thalamus and substantia nigra of the same side (fig. 2) (Kennedy *et al.*, 1975). Similar studies in the rat have led to comparable results and provided evidence on the basis of an evoked metabolic response of a 'mirror' focus in the motor cortex contralateral to the penicillin-induced epileptogenic focus (Collins, Kennedy, Sokoloff and Plum, 1976).

Effects of Decreased Functional Activity: Visual Deprivation in the Rat

Decrements in functional activity result in reduced rates of glucose utilization. In the rat, the visual system is 80 to 85 per cent crossed at the optic chiasma (Lashley, 1934; Montero and Guillery, 1968), and unilateral enucleation removes most of the sensory input due to either retinal stimulation by light or spontaneous retinal cell potentials to the central visual structures of the contralateral side. In the conscious rat studied twenty-four hours after unilateral enucleation, there are marked decrements in [^{14}C]DG uptake in the contralateral superior colliculus, lateral geniculate body, and visual cortex as compared to the ipsilateral side (fig. 3) (Kennedy *et al.*, 1975). These effects are observed whether the remaining eye is stimulated repetitively with a photoflash or the animal is maintained in normal room light. In the rat with both eyes intact, no asymmetry in the autoradiographs is observed (fig. 3).

Visual Deprivation in the Monkey

In animals with binocular visual systems, such as the Rhesus monkey, there is only approximately 50 per cent crossing of the visual pathways, and the structures of the visual system on each side of the brain receive equal inputs from both

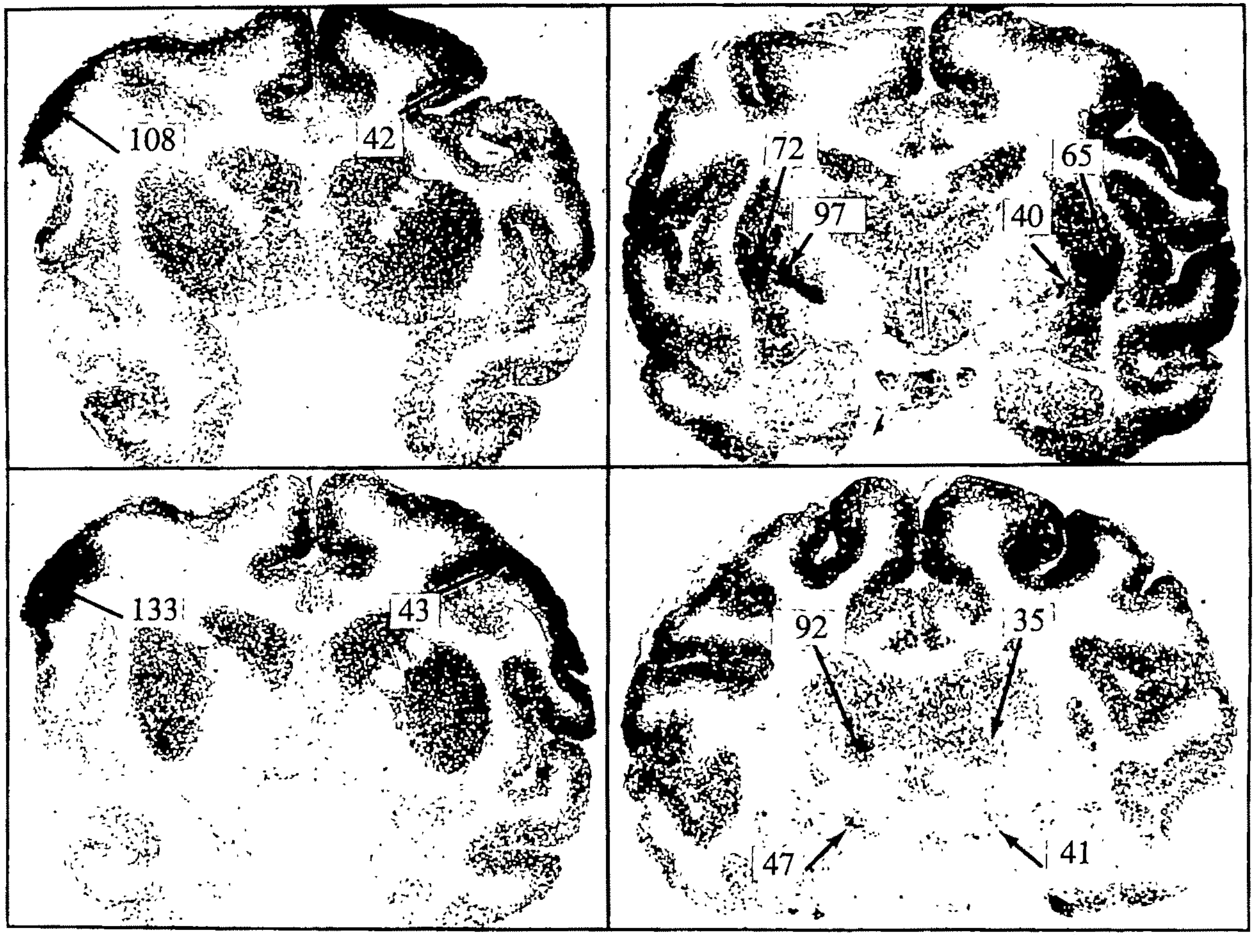

Fig. 2

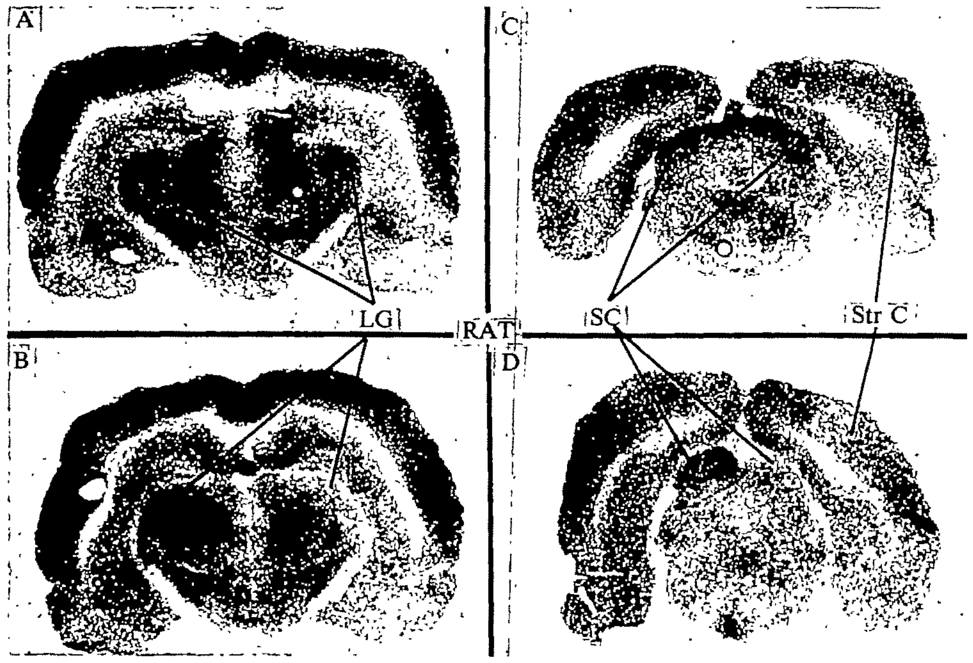

FIG. 3. Effects of unilateral enucleation on [^{14}C]deoxyglucose uptake in components of the visual system in the rat. In the normal rat with both eyes intact the uptakes in the lateral geniculate bodies (LG), superior colliculi (SC) and striate cortex (STR C) are approximately equal on both sides (A and C). In the unilaterally enucleated rat there are marked decreases in optical densities in the areas corresponding to these structures on the side contralateral to the enucleation (B and D). From Kennedy *et al.* (1975).

retinæ. Although each retina projects more or less equally to both hemispheres, their projections remain segregated and terminate in six well-defined laminæ in the lateral geniculates, three each for the ipsilateral and contralateral eyes (Hubel and Wiesel, 1968, 1972; Wiesel, Hubel and Lam, 1974; Rakic, 1976). This segregation is preserved in the optic radiations which project the monocular representations of the two eyes for any segment of the visual field to adjacent regions of Layer IV of the striate cortex (Hubel and Wiesel, 1968, 1972). The cells responding to the input of each monocular terminal zone are distributed transversely through the thickness of the striate cortex resulting in a mosaic of columns, 0.3 to 0.5 mm in width,

FIG. 2. Effects of focal seizures produced by local application of penicillin to motor cortex on local cerebral glucose utilization in the Rhesus monkey. The penicillin was applied to the hand and face area of the left motor cortex. The left side of the brain is on the left in each of the autoradiographs in the figure. The numbers are the rates of local cerebral glucose utilization in μmol/100 g tissue/min, calculated according to the operational equation presented in the text. Note the following: *upper left*, motor cortex in region of penicillin application and corresponding region of contralateral motor cortex; *lower left*, ipsilateral and contralateral motor cortical regions remote from area of penicillin applications; *upper right*, ipsilateral and contralateral putamen and globus pallidus; *lower right*, ipsilateral and contralateral thalamic nuclei and substantia nigra. From Kennedy *et al.* (1975).

alternately representing the monocular inputs of the two eyes. The nature and distribution of these ocular dominance columns have previously been characterized by electrophysiological techniques (Hubel and Wiesel, 1968), Nauta degeneration methods (Hubel and Wiesel, 1972), and by autoradiographic visualization of axonal and transneuronal transport of [^{3}H]proline- and [^{3}H]fucose-labelled protein and/or glycoprotein (Wiesel, Hubel and Lam, 1974; Rakic, 1976).

In order to examine the effects of functional activity on energy metabolism in the binocular visual system, three groups of monkeys with different conditions of visual input were studied: (1) intact binocular vision; (2) bilateral visual occlusion; (3) monocular visual occlusion. Visual occlusions were achieved either by enucleation or by insertion of opaque plastic discs in the appropriate eyes at the time of the surgical procedure for the insertion of the catheters, that is, two to four hours prior to the administration of the pulse of [^{14}C]DG. Animals with intact vision in one or both eyes were either exposed to the ambient light of the laboratory or surrounded by a rotating, illuminated, black-white, complex geometric pattern during the experimental procedure. The results were qualitatively similar with either method of visual occlusion and with or without the rotating geometric pattern. Experimental modification of the visual input produced consistent changes in the pattern of distribution of the rates of glucose consumption, all clearly visible in the autoradiographs, that coincided closely with the changes in functional activity expected from known physiological and anatomical properties of the binocular visual system (Kennedy *et al.*, 1976).

(1) *Normal binocular vision.* In animals with intact binocular vision no bilateral asymmetry was seen in the autoradiographs of the structures of the visual system (figs. 4A, 5A). The lateral geniculate bodies and oculomotor nuclei appeared to be of fairly uniform density and essentially the same on both sides (fig. 4A). The visual cortex was essentially the same on both sides (fig. 5A), but throughout all of Area 17 there was heterogeneous density distributed in a characteristic laminar pattern. At least four different levels of density could be readily discerned which could be correlated with the known cytoarchitectural layers of the striate cortex apparent in myelin- and thionin-stained sections (fig. 6). A wide band of relatively low but uniform density in the autoradiograph encompassed Layers I, II and III which could not be distinguished further on the basis of [^{14}C]deoxyglucose uptake (fig. 6). Layers IVa, IVb and IVc were clearly associated with high rates of glucose utilization as indicated by the density of the autoradiographic regions corresponding to them; Layers IVb and IVc were the most active, exhibiting the densest patterns of all the layers seen in the autoradiograph (fig. 6). When the autoradiograph is compared with the section stained for myelin, it appears that the line of Gennari lies within the layer with greatest metabolic activity (fig. 6). In Layer V there appears to be a fairly abrupt decline in density, but the activity in Layer VI is intermediate between those of Layers IV and V (fig. 6). These observations indicate that in animals with binocular visual input the rates of glucose consumption in the visual pathways are essentially equal on both sides of the brain and relatively

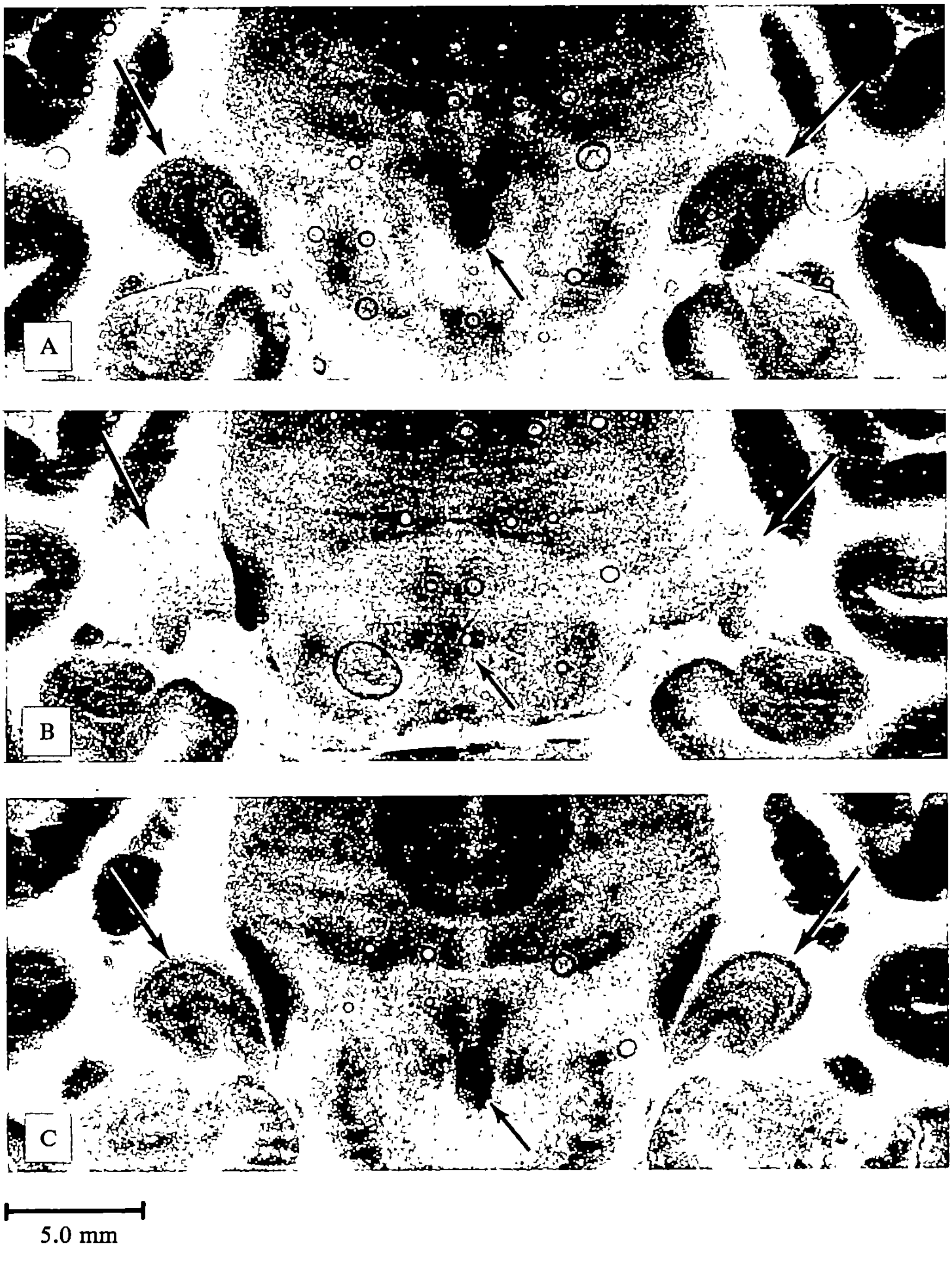

FIG. 4. Autoradiographs of coronal brain sections from Rhesus monkeys at the level of the lateral geniculate bodies. Large arrows point to the lateral geniculate bodies; small arrows point to oculomotor nuclear complex. A, animal with intact binocular vision. Note the bilateral symmetry and relative homogeneity of the lateral geniculate bodies and oculomotor nuclei. B, animal with bilateral visual occlusion. Note the reduced relative densities, the relative homogeneity, and the bilateral symmetry of the lateral geniculate bodies and oculomotor nuclei. C, animal with right eye occluded. The left side of the brain is on the left side of the photograph. Note the laminæ and the inverse order of the dark and light bands in the two lateral geniculate bodies. Note also the lesser density of the oculomotor nuclear complex on the side contralateral to the occluded eye. From Kennedy *et al.* (1976).

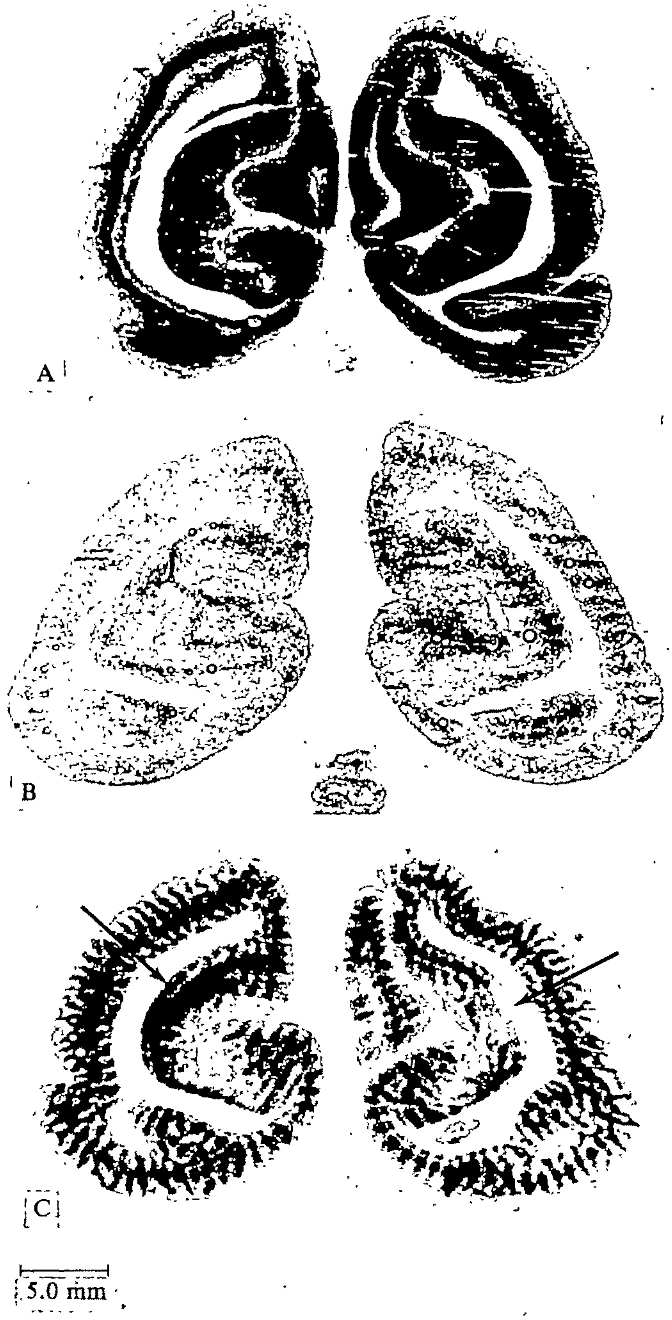

Fig. 5. Autoradiographs of coronal brain sections from Rhesus monkeys at the level of the striate cortex. A, animal with normal binocular vision. Note the laminar distribution of the density; the dark band corresponds to Layer IV. B, animal with bilateral visual deprivation. Note the almost uniform and reduced relative density, especially the virtual disappearance of the dark band corresponding to Layer IV. C, animal with right eye occluded. The half-brain on the left side of the photograph represents the left hemisphere contralateral to the occluded eye. Note the alternate dark and light striations, each approximately 0.3 to 0.4 mm in width, representing the ocular dominance columns. These columns are most apparent in the dark lamina corresponding to Layer IV but extend through the entire thickness of the cortex. The arrows point to regions of bilateral asymmetry where the ocular dominance columns are absent. These are presumably areas with normally only monocular input. The one on the left, contralateral to occluded eye, has a continuous dark lamina corresponding to Layer IV which is completely absent on the side ipsilateral to the occluded eye. These regions are believed to be the loci of the cortical representations of the blind spots (*see text*). From Kennedy *et al.* (1975); Kennedy *et al.* (1976).

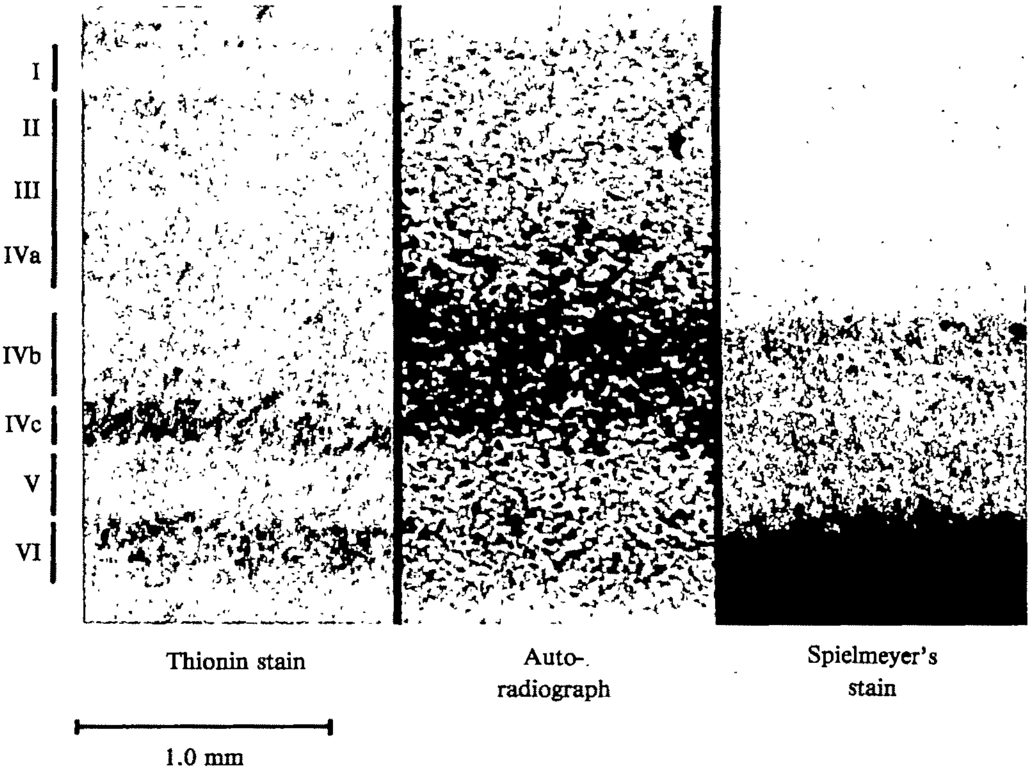

FIG. 6. Comparison of autoradiograph, thionin stain and myelin stain of a section of striate cortex from a monkey with intact binocular vision. The autoradiograph was made from the same section subsequently stained with thionin. An immediately adjacent section was stained for myelin with Spielmeyer's stain. The thionin stain distinguishes the cell-sparse Layers I, IVb, and V and the three cell-dense regions, Layers II, III and IVa (considered as one), Layer IVc, and Layer VI, according to Brodman's system. The dense zone in the autoradiograph traverses all of Layer IV and encompasses the stria of Gennari which is demarcated by the myelin stain. From Kennedy *et al.* (1976).

uniform in the oculomotor nuclei and lateral geniculate bodies, but markedly different in the various layers of the striate cortex. The most intense metabolic activity appears to be in sub-layers of Layer IV, (figs. 5A, 6), coinciding with the sites of termination of the geniculocortical projections on spine-bearing stellate cells (Hubel and Wiesel, 1972; Garey and Powell, 1971). Within each layer, or sub-layer, however, the metabolic activity appears to be relatively uniform throughout the extent of the cortex representing the various portions of the visual fields.

(2) *Bilateral visual deprivation.* Autoradiographs from the animals with both eyes occluded exhibited generally decreased labelling of all components of the visual system, but the bilateral symmetry was generally retained (figs. 4B, 5B), and the density within each lateral geniculate body was for the most part fairly uniform (fig. 4B). In the striate cortex, however, the marked differences in the densities of

the various layers seen in the animals with intact bilateral vision (fig. 5A) were virtually absent so that, except for a faint delineation of a band within Layer IV, the concentration of the label was essentially homogeneous throughout the striate cortex (fig. 5B).

(3) *Unilateral visual deprivation.* Autoradiographs from monkeys with only monocular input exhibited markedly different patterns from those described above. Both lateral geniculate bodies exhibited exactly inverse patterns of alternating dark and light bands corresponding to the known laminæ representing the regions receiving the different inputs from the retinæ of the intact and occluded eyes (fig. 4C). Bilateral asymmetry was also seen in the oculomotor nuclear complex; a lower density was apparent in the nuclei contralateral to the occluded eye (fig. 4C). In the striate cortex the pattern of distribution of the [^{14}C]deoxyglucose-6-phosphate appeared to be a composite of the patterns seen in the animals with intact and bilaterally occluded visual input. The pattern found in the former regularly alternates with that of the latter in columns orientated perpendicularly to the cortical surface (fig. 5C). The dimensions, arrangement, and distribution of these columns are identical to those of the ocular dominance columns described by Hubel and Wiesel (1968, 1972) and Wiesel, Hubel and Lam (1974). These columns reflect the interdigitation of the representations of the two retinæ in the visual cortex. Each element in the visual field is represented by a pair of contiguous bands in the visual cortex, one for each of the two retinæ or their portions that correspond to the given point in the visual fields. With symmetrical visual input bilaterally, the columns representing the two eyes are equally active and, therefore, not visualized in the autoradiographs (fig. 5A). When one eye is blocked, however, only those columns representing the blocked eye become metabolically less active, and the autoradiographs then display the alternate bands of normal and depressed activities corresponding to the regions of visual cortical representation of the two eyes (fig. 5C).

There can be seen in the autoradiographs from the animals with unilateral visual deprivation regions in the folded calcarine cortex that exhibit bilateral asymmetry (fig. 5C). The ocular dominance columns are absent on both sides, but on the side contralateral to the occluded eye this region has the appearance of visual cortex from an animal with normal bilateral vision, and on the ipsilateral side this region looks like cortex from an animal with both eyes occluded (fig. 5). These regions are the loci of the cortical representation of the blind spots of the visual fields and normally have only monocular input (Kennedy *et al.*, 1975). The area of the optic disc in the nasal half of each retina cannot transmit to this region of the contralateral striate cortex which, therefore, receives its sole input from an area in the temporal half of the ipsilateral retina. Occlusion of one eye deprives this region of the ipsilateral striate cortex of all input while the corresponding region of the contralateral striate cortex retains uninterrupted input from the intact eye. The metabolic reflection of this ipsilateral monocular input is seen in the autoradiographs in fig. 5C.

SUMMARY

A method has been developed to measure the rates of glucose utilization in the individual structural and functional components of the central nervous system. It can be applied to conscious as well as anæsthetized animals. The method is based on the use of [^{14}C]deoxyglucose as a tracer for glucose consumption. [^{14}C]Deoxyglucose-6-phosphate accumulates in the tissue in a mathematically definable relationship to the rate of the tissue's glucose utilization. The [^{14}C]deoxyglucose-6-phosphate concentrations in the various tissues of the nervous system are measured by a quantitative autoradiographic technique. The autoradiographs themselves are pictorial representations of the relative rates of glucose consumption in these tissues. Application of this method to rats and monkeys in various states of altered function demonstrates a clear and close relationship between the local levels of functional activity and energy metabolism. The method appears to be useful for mapping functional neural pathways on the basis of evoked metabolic responses (Plum, Gjedde and Samson, 1976).

REFERENCES

CAVENESS, W. F. (1969) Ontogeny of focal seizures. In: *Basic Mechanisms of the Epilepsies*. Edited by H. H. Jasper, A. A. Ward and A. Pope. Boston: Little, Brown and Co., pp. 517–534.

COLLINS, R. C., KENNEDY, C., SOKOLOFF, L. and PLUM, F. (1976) Metabolic anatomy of focal motor seizures. *Archives of Neurology, Chicago*, **33**, 536–542.

EKLÖF, B., LASSEN, N. A., NILSSON, L., NORBERG, K. and SIESJÖ, B. K. (1973) Blood flow and metabolic rate for oxygen in the cerebral cortex of the rat. *Acta Physiologica Scandinavica*, **88**, 587–589.

GAREY, L. J. and POWELL, T. P. S. (1971) An experimental study of the termination of the lateral geniculo-cortical pathway in the cat and monkey. *Proceedings of the Royal Society of London*, **179**, 41–63.

HUBEL, D. H. and WIESEL, T. N. (1968) Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, London*, **195**, 215–243.

—— —— (1972) Laminar and columnar distribution of geniculo-cortical fibers in the Macaque monkey. *Journal of Comparative Neurology*, **146**, 421–450.

KENNEDY, C., DES ROSIERS, M., JEHLE, J. W., REIVICH, M., SHARP, F. and SOKOLOFF, L. (1975) Mapping of functional neural pathways by autoradiographic survey of local metabolic rate with [^{14}C]deoxyglucose. *Science*, **187**, 850–853.

KENNEDY, C., DES ROSIERS, M. H., SAKURADA, O., SHINOHARA, M., REIVICH, M., JEHLE, J. W. and SOKOLOFF, L. (1976) Metabolic mapping of the primary visual system of the monkey by means of the autoradiographic [^{14}C]deoxyglucose technique. *Proceedings of the National Academy of Sciences of the United States of America*, **73**, 4230–4234.

—— SAKURADA, O., SHINOHARA, M., JEHLE, J. and SOKOLOFF, L. (1978) Local cerebral glucose utilization in the normal conscious Macaque monkey. *Annals of Neurology*, **4**, 293–301.

KETY, S. S. (1950) Circulation and metabolism of the human brain in health and disease. *American Journal of Medicine*, **8**, 205–217.

KETY, S. S. (1957) The general metabolism of the brain *in vivo*. In: *The Metabolism of the Nervous System*. Edited by D. Richter. London: Pergamon Press, pp. 221-237.

LANDAU, W. M., FREYGANG, W. H., Jr., ROWLAND, L. P., SOKOLOFF, L. and KETY, S. S. (1955) The local circulation of the living brain; values in the unanesthetized and anesthetized cat. *Transactions of the American Neurological Association*, **80**, 125-129.

LASHLEY, K. S. (1934) The mechanism of vision. VII. The projection of the retina upon the primary optic centers of the rat. *Journal of Comparative Neurology*, **59**, 341-373.

LASSEN, N. A. (1959) Cerebral blood flow and oxygen consumption in man. *The Physiological Review*, **39**, 183-238.

MONTERO, V. M. and GUILLERY, R. W. (1968) Degeneration in the dorsal lateral geniculate nucleus of the rat following interruption of the retinal or cortical connections. *Journal of Comparative Neurology*, **134**, 211-242.

NILSSON, B. and SIESJÖ, B. K. (1976) A method for determining blood flow and oxygen consumption in the rat brain. *Acta Physiologica Scandinavica*, **96**, 72-82.

PLUM, F., GJEDDE, A. and SAMSON, F. E. (1976) Neuroanatomical functional mapping by the radioactive 2-deoxy-D-glucose method. *Neurosciences Research Program Bulletin*, **14**, 457-518.

RAKIC, P. (1976) Prenatal genesis of connections subserving ocular dominance in the Rhesus monkey. *Nature, London*, **261**, 467-471.

REIVICH, M., JEHLE, J., SOKOLOFF, L. and KETY, S. S. (1969) Measurement of regional cerebral blood flow with antipyrine-[^{14}C] in awake cats. *Journal of Applied Physiology*, **27**, 296-300.

SCHMIDT, C. F., KETY, S. S. and PENNES, H. H. (1945) The gaseous metabolism of the brain of the monkey. *American Journal of Physiology*, **143**, 33-52.

SOKOLOFF, L. (1969) Cerebral circulation and behavior in man: strategy and findings. In: *Psychochemical Research in Man*. Edited by A. J. Mandell and M. P. Mandell. New York: Academic Press, pp. 237-252.

—— (1975) The [^{14}C]deoxyglucose method for the quantitative determination of local cerebral glucose utilization. In: *Blood Flow and Metabolism in the Brain*. Edited by A. M. Harper, W. B. Jennett, J. D. Miller and J. W. Rowan. Edinburgh: Churchill Livingstone, pp. 15.1-15.8.

—— (1976) Circulation and energy metabolism of the brain. In: *Basic Neurochemistry*. Second Edition. Edited by G. J. Siegel, R. W. Albers, R. Katzman and B. W. Agranoff. Boston: Little, Brown and Co., pp. 388-413.

—— (1977) Relation between physiological function and energy metabolism in the central nervous system. *Journal of Neurochemistry*, **29**, 13-26.

—— REIVICH, M., KENNEDY, C., DES ROSIERS, M. H., PATLAK, C. S., PETTIGREW, K. D., SAKURADA, O. and SHINOHARA, M. (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, **28**, 897-916.

WIESEL, T. N., HUBEL, D. H. and LAM, D. M. K. (1974) Autoradiographic demonstration of ocular dominance columns in the monkey striate cortex by means of transneuronal transport. *Brain Research, Amsterdam*, **79**, 273-279.

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THE ASYMMETRIC LATERALIZATION OF TACTILE EXTINCTION IN PATIENTS WITH UNILATERAL CEREBRAL DYSFUNCTION

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INTRODUCTION

MANY authors have noted that hemi-inattention is more severe or more frequently observed after lesions of the right hemisphere than the left (Brain, 1941; Critchley, 1949, 1953; Arrigoni and De Renzi, 1964; Gainotti, 1968; Costa, Vaughan, Horwitz and Ritter, 1969; Hécaen, 1969; Kinsbourne, 1970, Heilman and Valenstein, 1972; Albert, 1973; DeMyer, 1974; Oxbury, Campbell and Oxbury, 1974; Friedland and Weinstein, 1977; Gainotti, Caltagirone and Miceli, 1977). The evidence of others strongly suggests that the apparent asymmetric vulnerability of the right hemisphere is artifactual since untestable aphasics with left hemisphere damage cannot be evaluated (Battersby, Bender, Pollack and Kahn, 1956; Zarit and Kahn, 1974). However, on examination of the literature with reference to the more susceptible side of the body or extrapersonal space instead of the cerebral hemisphere, one finds a consistent, asymmetric distribution of inattention towards the left which cannot be explained on the basis of a biased selection of lateralized brain-damaged cases. For example, commissurotomized patients tested with bilateral simultaneous stimuli usually exhibit severe extinction of the left ear (Sparks and Geschwind, 1968; Milner, Taylor and Sperry, 1968; Springer and Gazzaniga, 1975; Efron, Bogen and Yund, 1977) or of the left visual field (Gazzaniga, Bogen and Sperry, 1967; Teng and Sperry, 1973). Furthermore, inattention to stimuli on the left has been reported after left (ipsilateral) cerebral lesions (Welman, 1969; Sparks, Goodglass and Nickel, 1970; Lynn, Benitez, Eisenbrey, Gilroy and Wilner, 1972; Albert, 1973; Schwartz, Marchok and Flynn, 1977), but we are not aware of any observations of right-sided inattention after right hemisphere injury. A lateralized proclivity for extinction of the left has also been observed in normal intact subjects (Kimura, 1961; McKeever and Huling, 1971). Whereas it may be difficult to make a case for hemispheric asymmetry in the manifestation of unilateral inattention, it may be possible to demonstrate that the left side of the body or of extrapersonal space is more susceptible to inattention, at least in the form of extinction, than the right side.

The extinction phenomenon itself is operationally distinguishable from unilateral neglect and other forms of hemi-attention in that a stimulus is not perceived *only when* a second stimulus is presented simultaneously—usually but not necessarily on the opposite side of the body. Neglect, on the other hand, does not require competing stimuli, as can most readily be shown in the non-visual modalities where secondary stimuli are easily controlled (Friedland and Weinstein, 1977). Unilateral neglect is manifest as a lack of responsivity to stimuli on one side of the body, in the absence of any sensory or motor deficit severe enough to account for the imperception. The two terms have been used interchangeably (Denny-Brown, Meyer and Horrenstein, 1952; Watson, Heilman, Cauthen and King, 1973; Springer and Gazzaniga, 1975), while some authors have proposed that extinction is a mild form of neglect (Denny-Brown and Banker, 1954; Kinsbourne, 1974*a*; Heilman and Watson, 1977) or that neglect is a severe case of extinction (Bender, 1977; Friedland and Weinstein, 1977). Since the relationship between extinction and neglect is largely unknown, findings obtained by one method should be applied to the other phenomenon only with extreme caution. This study is confined to the extinction phenomenon as defined above.

The fact that a perception can be extinguished by a simultaneous second stimulus suggests that the activity from the latter has blocked the first stimulus' access to the response mechanism. This model has been offered by Sparks and Geschwind (1968) as an explanation for the left-ear extinction observed in commissurotomized patients. Specifically, they propose that monaural, left-ear verbal information can be adequately reported by these patients because of ipsilateral connections to the left hemisphere; however, the crossed pathway from the right ear is prepotent in enjoining the left-hemisphere verbal-response mechanism. When a simultaneous input arrives from the right ear, the input from the subordinate ipsilateral pathway is overwhelmed by that from the stronger, crossed pathway at their confluence in the left hemisphere. In normals, the strength of the left-ear information is maintained by the crossed pathway to the right hemisphere and its subsequent relay into the left hemisphere via the corpus callosum.

In an earlier study of tactile extinction in the monkey, Eidelberg and Schwartz (1971) proposed that the disturbance resulted from a relative decrease in the sensory capacity of one input processing channel compared to that of a competing channel, as in the case of unilateral damage to somatosensory pathways or parietal cortex. Conceivably this view supplements the model of Sparks and Geschwind (1968) by suggesting that any degradation in the signal coming from one side of the body would weaken its control of the response mechanism, especially in the presence of a simultaneous, undegraded signal arriving at the same mechanism from another part of the body. It is important to recall here that the definition of extinction requires that each single stimulus alone is able to evoke the appropriate response.

The above model of sensory extinction implies that the phenomenon should be observed on the right as well as the left side of the body after unilateral damage to the relevant sensory mechanism. Since most tests for extinction require some verbal activity on the part of the subject (for example, understanding the instructions, or dealing with verbal test stimuli, or responding verbally), the left hemisphere must eventually be involved in mediation of both stimuli during a bilateral, simultaneous discrimination. An asymmetric bias is thus introduced in that the left-side stimulus must traverse a long, indirect route to the left hemisphere, in contrast to the right-side stimulus which proceeds directly to this hemisphere and undergoes local processing. The relatively longer route of the left-side stimulus, which includes fibres crossing from the right to the left hemisphere via the corpus callosum, would render such signals more liable to degradation as a result of naturally occurring cerebral lesions. According to the above model, tactile extinction of the left hand can occur after damage to its input and processing channel in the right hemisphere, or to the callosal system responsible for the inter-hemispheric transfer of the information from the right to the left hemisphere. Tactile extinction of the right hand would occur only after damage to its input channel and processing centres in the left hemisphere, and their connections to the near-by verbal response mechanisms. In a random selection of patients with brain damage, the model predicts more frequent extinction of the left side of the body due to its greater number of vulnerable cerebral sites.

In a recent study, using a sensitive test for tactile extinction, we found the expected disturbance on the contralateral side of the body in patients with damage to the right or left parietal lobe (Schwartz *et al.*, 1977). However, in a small subgroup of cases with cerebral pathology confined to one of the frontal lobes, tactile extinction was found only for the left side of the body. We have extended our earlier study in order to investigate the suitability of the above model, with special regard to the relationship between lateralization of tactile extinction and hemispheric damage.

METHOD

Subjects

All patients admitted to the Neurology-Neurosurgery Service of the Barrow Neurological Institute over a period of two years were screened for inclusion in this study. Two groups of patients were selected for detailed examination—those with unilateral, supratentorial pathology (that is, the 'experimental' group) and those with no evidence of neurological disorder above L1 of the spinal cord. The latter were treated as control subjects together with a number of volunteers not in hospital. Categorization into the particular groups of patients with brain damage was determined on the basis of case history, clinical examination, angiography, radionucleide or computerized axial tomography (CT) scans, and visualization during operation. Patients with negative laboratory findings were not considered in the data below. Other subjects were dropped from the study because of their lack of co-operation, dementia, inadequate level of consciousness, and the presence of severe aphasia or somatosensory deficits which precluded their identifying the test objects. However, a log was maintained which recorded the sex, age, handedness, and type and locus of lesion in these latter cases.

The screening process resulted in administration of the extinction test battery to 234 patients with radiographically verified unilateral cerebral pathology. The ages of the 133 males ranged from 13 to 80 years (mean = 54); the 101 females ranged from 12 to 87 years (mean = 54). The control group consisted of 175 subjects; the 80 males ranged in age from 22 to 79 years (mean = 44), and the 95 females ranged from 17 to 74 years (mean = 52). The percentages of the patients with brain damage and the control subjects who were not right handers were 11 per cent and 12 per cent, respectively.

Procedure

Tactile extinction was assessed in each subject by the Quality Extinction Test. The Quality Extinction Test has been described in detail elsewhere (Schwartz, Marchok and Flynn, 1977). Briefly, it consists of two sets of various common materials such as sandpaper, wire mesh, carpeting, tin foil, velvet material, and a paint roller. One set consists of test items each of which is made up entirely of one of the materials ('whole' items), and a second set consists of items made up of two different materials side-by-side ('half-and-half' items). Each test item is brushed against the subject's outstretched fingers so that both hands are stimulated sumultaneously. Stimulation with the half-and-half set is arranged so that a different material stimulates each hand at the same time. Before the test the subject is shown only the whole items, allowed to examine them, and instructed in their names for later identification by touch. He is also told that he will be touched on both hands at the same time, that he may feel two different materials at the same time, and to report what he feels. The subject is then blindfolded and tested on each hand alone with each material in order to ensure that single stimulation of the separate hands is adequately perceived. Both hands are then tested with the whole and the half-and-half items in counterbalanced order.

In scoring the Quality Extinction Test, an extinction trial was recorded if the subject named only one material when in fact two had been presented. The total Quality Extinction Test score for each subject was derived by subtracting the number of omissions made by the more accurate hand from the number of omissions made by the other hand and converting the difference into a percentage. Errors in naming were not scored. Any score above 0 reflects the relative deficiency of one hand in detecting its stimuli; scores above 0 are therefore always expressed in association with the particular hand which made the most omissions.

Most of the subjects were also tested for somatosensory functions including two-point thresholds, graphæsthesia, stereognosia, and depth æsthesiometrics.

Radiographic evaluations were made by one of us (R.E.F.) without knowledge of the patient's test scores.

RESULTS

The data from the cerebrally intact control group were examined first in order to derive criteria for the classification of pathological extinction scores; the results are shown in Table 1. A left-side extinction bias was noted among control subjects with no brain damage; that is, a slightly greater proportion of controls yielded a left extinction score than a right (34.2 per cent v 24.5 per cent; $X^2 = 2.8$, df = 1, $0.10 > P > 0.05$). The asymmetric tendency towards extinction of the left side is also reflected by the higher mean left Quality Extinction Test score ($t = 2.93$; SD = 5.75, df = 109, $P < 0.01$). An analysis of the individual control scores revealed that less than 3 per cent achieved a left Quality Extinction Test of 24 or higher, or a right Quality Extinction Test of 12 or higher. These scores were arbitrarily adopted as the criteria cut-off scores for classifying a Quality Extinction Test result as representing true extinction or not.

TABLE 1. RESULTS OF QUALITY EXTINCTION TEST OF CONTROL GROUP

	Left extinc. scores	*Right extinc. scores*	*Zero extinc. scores*	*Totals*
N	60	43	72	175
%	34.2	24.5	41.1	100
Mean	9.85	6.65	0	—

The over-all distribution of pathological and insignificant extinction among the 234 testable patients (that is, patients not severely aphasic, anæsthetic, etc.) is shown in Table 2. Approximately 70 per cent of the right brain-damaged (RBD) cases extinguished as compared to 59 per cent of the left brain-damaged (LBD) group; the difference however was not significant ($X^2 = 2.94$, df = 1, $0.10 > P > 0.05$). Although these data suggest a tendency towards more frequent extinction after right than after left hemisphere lesions, 87 LBD patients were also encountered but were untestable, mostly because of severe aphasia (N = 83), as compared to 31 RBD patients who were untestable because of hypæsthesia. Since the number of extinguishers among these untestables cannot be determined, we must conclude that there is no evidence for a significant hemispheric bias when considering damage to each hemisphere as a whole. As will be shown below, however, the factor of lesion laterality becomes important when we compare specific regions within each hemisphere.

In regard to the lateralization of the extinction sign, the left side of the body was extinguished more than 2.4 times as often as the right side (Table 2). We would expect only 1.3 times as many left-side extinguishers, reflecting the extinction ratio between the LBD and RBD groups shown in Table 2. This expectation, however, assumes that the extinction sign is consistently on the side contralateral to the lesion. That this assumption is invalid is demonstrated by the fact that the RBD and LBD groups were not equivalent in terms of the frequency of contralateral versus ipsilateral extinction; the LBD group exhibited significantly more ipsilateral (left side) extinction than the RBD group ($X^2 = 27.64$, df = 1, $P < 0.001$). The greater incidence of left-side extinction appears to be a real phenomenon since (*a*) the percentage of LBD and RBD patients who extinguished did not significantly differ, and (*b*) only the LBD group showed a significant amount of ipsilateral extinction. The high proportion of left-side extinction (33 per cent) among the LBD group, added to the almost exclusively left-side extinction rate among the RBD group, results in a greater total incidence of left-side extinction.

TABLE 2. DISTRIBUTION OF LEFT, RIGHT AND INSIGNIFICANT EXTINCTION SCORES AMONG THE LBD AND RBD PATIENTS

	LBD	*RBD*	*Totals*
Left extinction	22	85	107
Right extinction	44	1	45
No extinction	46	36	82
Totals	112	122	234

It may again be argued that the greater left-side extinction rate is spurious because of exclusion of LBD aphasics; if the aphasics were to show a high contralateral extinction rate, then the number of right extinguishers would be increased relative to the number of left extinguishers and possibly eliminate the difference shown in Table 2. We sought to test this possibility by examining the effect of projecting all 87 untestable LBD patients as if they had extinguished the right side, thereby raising the total number of LBD cases to 199. In order to counterbalance the effect of lesion lateralization, the RBD group was also increased to 199, but the additional, hypothetical cases were distributed among the left, right, and zero extinction categories in the respective proportions as empirically determined in Table 2. Despite the projection of more frequent extinction among the LBD group, and despite the projection of all LBD untestables as if extinguishing the right side, the frequency of left-side extinction would still exceed that of the right (160 v 133, respectively).

Two further points should be noted. First, the estimated incidence of extinction of the left side may be even higher than projected above since not all the severe aphasics would be assumed to extinguish their contralateral as opposed to their ipsilateral side. This is indicated by the fact that the *testable* aphasics, shown in Table 3, manifested left (ipsilateral) extinction at a rate comparable to the LBD group as a whole (22 per cent and 19 per cent respectively). Secondly, Table 2 does not take into account the hand preference or hemispheric dominance of the patients. Theoretically, the inclusion of left-handers with right hemisphere speech representation would tend to decrease rather than increase the observed asymmetry. We will treat the relationship between hand-preference and extinction in a future communication.

TABLE 3. DISTRIBUTION OF TESTABLE LBD APHASICS BY EXTINCTION SIDE AND LESION LOCUS

Lesion locus	*Left extinc.*	*Right extinc.*	*No extinc.*
Frontal	5	0	2
Fronto-parietal	1	6	4
Temporal and fronto-temporal	1	2	2
Parietal, parieto-temporal, parieto-fronto-temporal	2	13	3
Totals	9	21	11

The location of the lesion sites was classified separately and without knowledge of the test performance for all 234 patients. The main bases for localization were CT scans, angiograms, and visualization during operation. Broad classifications were required because of the lack of definitive landmarks in these sources; the resulting categories and their associated frequencies of left and right extinction are shown in Table 4.

TABLE 4. DISTRIBUTION OF EXTINCTION AS A FUNCTION OF LESION LOCUS

	LBD			*RBD*		
Lesion locus	*Left extinc.*	*Right extinc.*	*No extinc.*	*Left extinc.*	*Right extinc.*	*No extinc.*
Frontal	11	0	11	5	1	15
Fronto-parietal	5	14	7	25	0	5
Fronto-temporo-parietal	3	8	1	6	0	0
Fronto-temporal	2	2	2	0	0	0
Parietal	0	7	10	26	0	3
Parieto-temporo-occipital	1	11	4	23	0	4
Temporal	0	2	10	0	0	6
Occipital	0	0	1	0	0	3

The data in Table 4 agree with the general view that tactile extinction is a prominent sign of parietal lobe disease. Approximately 79 per cent of all patients with damage *including* the parietal area exhibited significant extinction, while patients with varying degrees of frontal lobe injury, the next most prominent group showed a 67 per cent extinction rate. Considering those patients with damage presumably confined to the parietal or the frontal lobes, a significantly greater extinction rate is still seen among the former group (72 per cent v 40 per cent, respectively; $X^2 = 8.10$, df $= 1$, $P < 0.01$). Only 16 per cent of the small number of patients with isolated temporal lobe lesions extinguished; the rate reached 85 per cent when temporal lobe involvement was combined with parietal damage.

The data in Table 4 also suggest the source for the preponderance of left-side extinction. Whereas extinction after damage to the right hemisphere consistently appears on the contralateral side of the body, regardless of the lesion locus, a different pattern emerges with damage to the left hemisphere as the lesion locus progresses from the posterior to the anterior regions. Extinction of the contralateral side only was seen among the 17 patients with focal parietal pathology in the left hemisphere; as the lesion involved more of the frontal and less of the parietal lobe, the extinction sign tended to shift from the contralateral to the ipsilateral hand. Thus, the left hemisphere is characterized by contralateral extinction after parietal lesions and ipsilateral extinction after frontal lesions, in contrast to the right hemisphere where contralateral extinction is the rule. Furthermore, these data demonstrate that ipsilateral extinction is primarily a function of left frontal lesions.

Table 4 also indicates hemispheric asymmetry in regard to the role of the parietal lobes. RBD patients with lesions restricted to the parietal region extinguished more than twice as often as comparable parietal patients in the LBD group (90 per cent v 41 per cent respectively). A selective bias due to exclusion of LBD aphasics does not seem to be a factor in this asymmetry. The distribution of lesion loci among the untestable LBD patients is shown in Table 5. Only 7 severe aphasics with focal damage of the left parietal lobe were noted; if these 7 cases were projected as extinguishers and added to their testable counterparts, the right parietals would still show a significantly greater extinction rate (58 per cent v 90 per cent; $X^2 = 5.37$, $df = 1$, $P < 0.05$).

Damage to the left or right frontal lobes also tended to produce asymmetric effects, but the differences were not significant. Lesions in the left frontal area produced an extinction rate of 50 per cent and a mean Quality Extinction Test of 26.3, compared to an extinction rate of 40 per cent and a mean Quality Extinction Test of 18.8 for the subjects with damaged right frontal lobe.

TABLE 5. DISTRIBUTION OF LBD UNTESTABLE PATIENTS ACCORDING TO LESION LOCUS

	No. of cases	
Locus of lesion	*Aphasic*	*Hypæsthetic only*
Frontal	8	—
Fronto-temporal	5	—
Fronto-parietal	19	3
Fronto-temporal-parietal	18	—
Parietal	7	1
Parieto-temporo-occipital	20	—
Temporal	6	—

The extinction model presented earlier suggests that intercortical connections from the right to the left hemisphere are vital for verbal reporting of stimuli applied to the left hand, and that such information would be vulnerable when damage occurs anywhere along these connections. As Table 4 shows, a high proportion of patients with isolated frontal lesions extinguished the left side, in contrast to all the other anatomical groups which are characterized by contralateral extinction. This observation suggested that some of the proposed interhemispheric fibres pass through the frontal lobes on their way in and out of the corpus callosum. Accordingly we hypothesized that frontal cases with evidence of callosal involvement would be more likely to show extinction and would show higher extinction scores than those without callosal involvement.

The radiographic material from the 43 cases in the frontal group were classified by an independent observer (R.E.F.) according to whether the lesion was situated so as to affect the corpus callosum. The CT scan sections, which had been obtained at approximately a 20 to 30 degrees angle to Reid's baseline, were compared with similarly cut sections of the brain as illustrated by New and Scott (1975). Abnormal densities extending into the region of white matter immediately adjacent to the callosum, as well as into the callosum itself, were classified as callosal 'hits'. Pressure effects in the same regions, as determined from angiograms and CT scans, were not considered hits.

The sorting procedure resulted in identifying 14 frontal cases with lesions suspected of involving the callosum, and 9 cases with lesions too far removed to affect the callosum (Table 6); the remaining cases were doubtful and did not allow a firm decision. The relationship between extinction and callosal damage was significant ($X^2 = 3.87$, df $= 1$, $P < 0.05$). In addition, a comparison of the Quality Extinction Test scores for the two groups revealed that the patients with damage to the callosum had consistently higher extinction scores than the patients with an intact callosum (Mann-Whitney $U = 21.5$, $P < 0.02$). Thus the data tend to support the view that the asymmetric extinction pattern shown by the frontal group is associated with callosal damage, at least in part.

TABLE 6. DISTRIBUTION OF EXTINCTION AMONG FRONTAL DAMAGED PATIENTS IN RELATION TO CALLOSAL INVOLVEMENT

	Callosal hit	*Callosal miss*
Left extinction	9	2
No extinction	5	7

Somatosensory Deficits and Tactile Extinction

The model described in the Introduction suggests that degradation of somatosensory input to one hemisphere renders the signal from the contralateral side of the body at a disadvantage in competing with the intact signal for the final response mechanism; it would therefore predict an association between sensory deficits and tactile extinction. Fifty-two patients (26 LBD, 26 RBD) were also tested with a battery of standard somatosensory tests: 2-point thresholds, tactile depth discrimination, graphæsthesia, and stereognosis. A somatosensory deficit was recorded when performance on any of these tests was impaired relative to the performance of intact control subjects. The results shown in Table 7 indicate a significant relationship between tactile extinction and somatosensory deficits as measured here ($X^2 = 11.27$, df $= 1$, $P < 0.001$). Severity of extinction was significantly correlated with the number of sensory tests showing impairment ($r = 0.56$; $P < 0.01$), and abnormal 2-point threshold was the most frequent sign; otherwise, no consistent pattern of sensory deficits emerged in this group.

TABLE 7. RELATIONSHIP BETWEEN EXTINCTION AND SOMATOSENSORY DEFICITS

	Extinction	*No extinction*
Sensory deficits	23	4
No sensory deficits	9	16

DISCUSSION

In his 1949 paper, Critchley observed that tactile extinction does not depend upon whether the diseased hemisphere is the dominant (left) or subordinate (right) hemisphere, although he noted a slight bias in favour of the right. Our data agree with Critchley's view; the RBD group studied here tended to extinguish more than the LBD group, but the difference was not significant. Possibly even this slight asymmetry may disappear when tests are developed which will enable examination of severe aphasics.

Our data, however, support the concept of hemispheric asymmetry when the subregions within each hemisphere are considered. Damage restricted to the right parietal lobe resulted in more instances of tactile extinction than injury to the left parietal lobe, even under the extreme assumption that all the untestable aphasics with focal parietal damage in our relatively unselected population would also have extinguished if tested. This trend toward asymmetry persisted, although in diminishing degree, when combined lesions which included the parietal zone were compared. It may appear contradictory to suggest that the two hemispheres do not significantly differ in their association with the extinction sign and at the same time to argue that damage to the right parietal lobe is more conducive to extinction than damage to the left. The discrepancy could be resolved if some region in the left hemisphere showed the opposite relationship with its homologous area in the right hemisphere. Table 4 suggests such a possibility: left frontal damage resulted in tactile extinction more frequently than did right frontal damage, although the difference found here was not significant. Evidently the higher frequency of extinction among the left frontal group partially compensates for the asymmetry created by the right parietal group, with the result that the LBD and RBD groups as a whole show no significant difference in extinction rate.

In contrast to the slight hemispheric asymmetry in production of tactile extinction, the left side of the body showed a clear susceptibility. This left-side susceptibility cannot be due entirely to the greater efficacy of right parietal lesions, since 50 per cent of the LBD patients who extinguished did so on the left (ipsilateral) side, as compared to less than 2 per cent of the RBD extinguishers who extinguished the right (ipsilateral) side (Table 2). It is also unlikely that the selective exclusion of severe aphasics contributed toward the asymmetrical distribution of extinction scores, since the extinguished sides of the testable aphasics were distributed in approximately the same proportions as the LBD group as a whole. We conclude that tactile extinction, as measured by the Quality Extinction Test, is predominantly a left-side phenomenon.

The finding that tactile extinction of the left side is more frequent than of the right (in a predominantly right-handed human population) may have some heuristic value in theorizing about possible mechanisms. We will consider only a few.

Kinsbourne (1970; 1974*b*) has proposed an explanation for the preponderance of left-side neglect which may also apply to extinction. Activation of the left (speech) hemisphere by the verbal requirements of the testing procedure, according to Kinsbourne, results in increased orientation to the right side of the body or space. Countervailing influences from the right hemisphere would be diminished by damage to the latter, further enhancing orientation to the right: lesions of the left hemisphere would be compensated by increased activation of the remaining left structures through verbal activity. Kinsbourne's activation factor may account for the high incidence of left side neglect mentioned in our Introduction, and by extension, for the preponderance of left-side extinction in our parietal lobe patients, but in its present form it does not explain the left-side ipsilateral extinction with LBD seen here, nor the consistent reports of left-ear extinction in split callosum patients during dichotic listening (Milner *et al.*, 1968; Sparks and Geschwind, 1968; Springer and Gazzaniga, 1975).

A similar theory has been offered by Heilman and Watson (1977). These authors proposed that extinction is a mild form of neglect, and that unilateral neglect results from impairment to a cortical-reticular-limbic loop which is responsible for orientating responses to the contralateral side. This model does not account for the asymmetric distribution of neglect as well as does Kinsbourne's activation theory, nor does it predict the predominance of left-side extinction after frontal damage or commissurotomy.

Denny-Brown and his colleagues (1952, 1954) have made extensive studies on a few patients and concluded that extinction is a consequence of an inability to integrate spatial sensory stimuli (amorphosynthesis). The data presented here on the human, and reported earlier on the monkey (Eidelberg and Schwartz, 1971) confirm that somatosensory deficits are associated with tactile extinction, but the contention of Denny-Brown also has difficulty accounting for the asymmetric lateralization of the extinction sign. This is especially illustrated by several of our patients with left frontal or fronto-parietal lesions who demonstrated typical right-sided sensory impairment but who extinguished the left side.

Studies in the monkey led Eidelberg and Schwartz (1971) to propose that a damaged input or processing channel is handicapped when competing with a contralateral simultaneous signal for expression. The imbalance in the relative strengths of the two signals arriving at a final common response mechanism results in reporting only the signal from the intact side. The finding of asymmetric extinction in humans, however, suggests that this explanation is incomplete. By extending and combining the concepts of both Eidelberg and Schwartz (1971) and Sparks and Geschwind (1968) we can offer a model which agrees with the findings. According to this model, impairment of one sensory channel increases the likelihood that its information will be occluded by simultaneous activity in the intact channel at their junction with the response mechanism. The nature and locus of the hypothetical response mechanism cannot be specified at this time, but it is assumed to vary as a function of several factors, especially with the reporting requirements of the test. In the case of humans where the extinction test usually includes some verbal component, it is further assumed to be closely associated with the speech areas in the left hemisphere. This arrangement in the human makes the left hand information more vulnerable than the right, as proposed by Sparks and Geschwind (1968) and outlined in the Introduction above. Thus, at least two factors may contribute to the degradation of a signal channel *vis à vis* a simultaneously competing one—injury to its sensory input and processing mechanisms, and injury to the pathway carrying the processed information to the response centre.

Other factors must also be involved in tactile extinction, as suggested by the fact that the presence or absence of sensory deficits did not completely predict whether extinction will be manifest (Table 7). Patients with spinal disease generally show less tactile extinction than those with cerebral damage (Shapiro and Feldman, 1952), even in the presence of sensory deficits. Sensory impairment strongly suggests damage to the somatosensory system and degradation of the tactile signal which, according to our model, should lead to extinction. However, the separate components of the primate's afferent pathway do not mediate identical tactile functions (Azulay and Schwartz, 1975) and are differentially involved in the extinction phenomenon (Eidelberg and Schwartz, 1971). It is therefore possible that measurement of other tactile functions not included in our battery would have yielded a higher correlation between sensory deficits and extinction. It is also worth considering whether lesions affecting components carrying processed tactile information (that is, association areas and their projections to the response mechanism) may be more effective in producing extinction than damage to the afferent components in the spinal cord and cortical primary projection area which carry relatively unprocessed information. This possibility may be a factor not only in the lack of complete concordance between sensory deficits and extinction, but might also apply to the LBD patients with sensory deficits on the right side but extinguished the left. Such patients would then be suspected of harbouring critical lesions in the white matter projecting to the response mechanism.

The data suggest some additional refinements of the model. Studies in subhuman primates have failed to identify direct interhemispheric connections between the cortical somatosensory hand areas and the opposite hemisphere (Pandya and Vignolo, 1968, 1969; Jones and Powell, 1969; but *see* Eidelberg and Jenkins, 1966). Furthermore, patients who have undergone commissurotomy cannot verbally identify objects palpated by the left hand (Gazzaniga, 1970). These considerations imply that left-hand information normally reaches the left hemisphere by indirect cerebral pathways which arise in the postcentral gyrus of the right hemisphere, then relay to other ipsilateral areas before crossing in the callosum. The fact that frontal lesions, particularly those encroaching on the anterior corpus callosum, may result in predominantly left-side extinction suggests that these structures contain one of the main pathways from the cortical hand area of the right hemisphere to the hypothesized response mechanism in the left hemisphere. Pandya and Kuypers (1969) and Jones and Powell (1970) have described intrahemispheric connections from the postcentral gyrus to area 5, from the latter to area 7 and from both to areas 6 and 46 in the frontal lobe of the monkey. Interhemispheric projections from these latter regions, crossing via the anterior corpus callosum to the opposite hemisphere, have also been identified (Pandya, Karol and Heilbronn, 1971), although there is no evidence as yet that these connections represent the hands (Karol and Pandya, 1971). Other pathways between the posterior parietal lobe and the opposite hemisphere cross in the trunk of the corpus callosum; these connections may account for the ability of patients with section of the anterior callosum to name objects palpated with their left hand (Gordon, Bogen and Sperry, 1971).

The widespread distribution of the hand-area projections in the right hemisphere, as indicated in the above model, also suggests an explanation for the parietal lobe asymmetry in extinction. By contrast, hand-area projections in the left hemisphere would comprise a more compact system since they must travel only a short distance to the speech areas, some of which have been identified in the parietal lobe itself (Ojemann and Whitaker, 1978). A relatively widespread anatomical system in the right parietal lobe would be more likely to receive damage from random lesions than a constricted system in the left parietal lobe. Semmes (1968) has proposed that sensorimotor capacities are represented differently in the two hemispheres, tending to be diffusely organized in the right hemisphere but focally represented in the left. The model for tactile extinction presented here invokes a similar dichotomy, but is more parsimonious in that it is based primarily on anatomical rather than on functional considerations.

SUMMARY

Two hundred and thirty-four patients with unilateral cerebral pathology and 175 control subjects were examined with a sensitive test for tactile extinction. Damage to the right hemisphere was associated with extinction slightly (but not significantly) more often than damage to the left hemisphere; the asymmetry may be due to selective exclusion of aphasics with damage to the left hemisphere. Extinction of the left side of the body, however, was significantly more common than of the right side; this asymmetry could not be accounted for by exclusion of untestable aphasics, but was a consequence of frequent ipsilateral (left side) extinction among the group with damage to the left hemisphere while the group with damage to the right hemisphere extinguished the contralateral (left) side almost exclusively. Although the hemispheres as a whole did not differ in their association with extinction, lesions in the right parietal lobe were significantly more effective in producing extinction than lesions in the left; in both cases the contralateral side of the body was affected. By contrast, lesions in the left frontal lobe were moderately but not significantly more effective in producing extinction than right frontal damage; in almost all these cases the left side of the body was affected, regardless of which frontal lobe was damaged. A relationship between extinction and pathology in the vicinity of the anterior callosum, as determined from CT scan and angiography, was found among the frontal cases.

We propose an anatomical model to explain tactile extinction and its asymmetric characteristics in the human. During the extinction tests a response mechanism in the left (speech) hemisphere bases its perceptual output on the relative strengths of two simultaneous sensory inputs. Damage at any point in the

channel from the periphery to the response mechanism weakens one signal in comparison to the other, resulting in a response bias favouring the stronger stimulus. Tactile information from the left hand, after reaching the somatosensory zone in the right hemisphere, is transmitted to the left hemisphere by a diffuse, widespread network including the frontal lobes and the anterior callosum. This anatomical arrangement renders left-hand information more vulnerable to chance lesions than right-hand information, which has direct access to the response mechanism via a more compact projection system.

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REFERENCES

ALBERT, M. L. (1973) A simple test of visual neglect. *Neurology, Minneapolis*, **23**, 658-664.

ARRIGONI, G. and DE RENZI, E. (1964) Constructional apraxia and hemispheric locus of lesion. *Cortex*, **1**, 170-197.

AZULAY, A. and SCHWARTZ, A. S. (1975) The role of the dorsal funiculus of the primate in tactile discrimination. *Experimental Neurology*, **46**, 315-332.

BATTERSBY, W. S., BENDER, M. B., POLLACK, M. and KAHN, R. L. (1956) Unilateral spatial agnosia ('inattention') in patients with cerebral lesions. *Brain*, **79**, 68-92.

BENDER, M. B. (1977) Extinction and other patterns of sensory inattention. In: *Hemi-inattention and Hemispheric Specialization*. Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 107-110.

BRAIN, W. R. (1941) Visual disorientation with special reference to lesions of the right cerebral hemisphere. *Brain*, **64**, 244-272.

COSTA, L. D., VAUGHAN, H. G., HORWITZ, M. and RITTER, W. (1969) Patterns of behavioral deficit associated with visual spatial neglect. *Cortex*, **5**, 242-263.

CRITCHLEY, M. (1949) The phenomenon of tactile inattention with special reference to parietal lesions. *Brain*, **72**, 538-561.

—— (1953) *The Parietal Lobes*. New York: Hafner, pp. 391-405.

DEMYER, W. (1974) *Technique of Neurological Examination*. Second edition. New York: McGraw-Hill, pp. 317-318, 347.

DENNY-BROWN, D. and BANKER, B. Q. (1954) Amorphosynthesis from left parietal lesions. *AMA Archives of Neurology and Psychiatry*, **71**, 302-313.

—— MEYER, J. S. and HORRENSTEIN, S. (1952) The significance of perceptual rivalry resulting from parietal lesion. *Brain*, **75**, 433-471.

EFRON, R., BOGEN, J. E. and YUND, E. (1977) Perception of dichotic chords by normal and commissurotomized human subjects. *Cortex*, **13**, 137–149.

EIDELBERG, E. and JENKINS, I. (1966) Organization of somatic sensory mechanisms in the macaque cerebral cortex. *Electroencephalography and Clinical Neurophysiology*, **21**, 452–460.

—— and SCHWARTZ, A. S. (1971) Experimental analysis of the extinction phenomenon in monkeys. *Brain*, **94**, 91–108.

FRIEDLAND, R. P. and WEINSTEIN, E. A. (1977) Hemi-inattention and hemisphere specialization: introduction and historical review. In: *Hemi-inattention and Hemisphere Specialization.* Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 1–31.

GAINOTTI, G. (1968) Les manifestions de négligence and inattention pour l'hémispace. *Cortex*, **4**, 64–91.

—— CALTAGIRONE, C. and MICELI, G. (1977) Poor performance of right brain-damaged patients on Raven's Coloured Matrices: derangement of general intelligence or of specific abilities? *Neuropsychologica*, **15**, 675–680.

GAZZANIGA, M. S. (1970) *The Bisected Brain.* New York: Appleton-Century-Crofts, pp. 81–84.

—— BOGEN, J. E. and SPERRY, R. W. (1967) Dyspraxia following division of the cerebral commissures. *Archives of Neurology, Chicago*, **16**, 606–612.

GORDON, H. W., BOGEN, J. E. and SPERRY, R. W. (1971) Absence of deconnection syndrome in two patients with partial section of the neocommissures. *Brain*, **94**, 327–336.

HÉCAEN, H. (1969) Aphasic, apraxic and agnostic syndromes in right and left hemisphere lesions. In: *Handbook of Clinical Neurology.* Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland, Vol. IV, pp. 291–311.

HEILMAN, K. M. and VALENSTEIN, E. (1972) Frontal lobe neglect in man. *Neurology, Minneapolis*, **22**, 660–664.

—— and WATSON, R. T. (1977) Mechanisms underlying the unilateral neglect syndrome. In: *Hemi-inattention and Hemisphere Specialization.* Edited by E. A. Weinstein and R. P. Friedland. New York: Raven Press, pp. 93–106.

JONES, E. G. and POWELL, T. P. S. (1969) Connections of the somatic sensory cortex of the rhesus monkey. II. Contralateral cortical connexions. *Brain*, **92**, 717–730.

—— —— (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93**, 793–820.

KAROL, E. A. and PANDYA, D. N. (1971) The distribution of the corpus callosum in the rhesus monkey. *Brain*, **94**, 471–486.

KIMURA, D. (1961) Cerebral dominance and the perception of verbal stimuli. *Canadian Journal of Psychology*, **15**, 166–171.

KINSBOURNE, M. (1970) A model for the mechanism of unilateral neglect of space. *Transactions of the American Neurological Association*, **95**, 143–146.

—— (1974*a*) Lateral interactions in the brain. In: *Hemisphere Disconnection and Cerebral Function.* Edited by M. Kinsbourne and W. L. Smith. Springfield, Illinois: C. C. Thomas, pp. 239–259.

—— (1974*b*) Mechanisms of hemispheric interaction in man. In: *Hemisphere Disconnection and Cerebral Function.* Edited by M. Kinsbourne and W. L. Smith. Springfield, Illinois: C. C. Thomas, pp. 260–285.

LYNN, G. E., BENITEZ, J. T., EISENBREY, A. B., GILROY, J. and WILNER, H. I. (1972) Neuroaudiological correlates in cerebral hemisphere disease. *Audiology*, **11**, 115–134.

MCKEEVER, W. F. and HULING, M. D. (1971) Lateral dominance in tachistoscopic word recognition performance obtained with simultaneous bilateral input. *Neuropsychologia*, **9**, 15–20.

MILNER, B., TAYLOR, L. and SPERRY, R. W. (1968) Lateralized suppression of dichotically presented digits after commissural section in man. *Science*, **161**, 184–186.

NEW, P. F. J. and SCOTT, W. R. (1975) *Computed Tomography of the Brain and Orbit*. Baltimore: Williams and Wilkins, pp. 54–115.

OJEMANN, G. A. and WHITAKER, H. A. (1978) Language localization and variability. *Brain and Language*, **6**, 239–260.

OXBURY, J. M., CAMPBELL, D. C. and OXBURY, S. M. (1974) Unilateral spatial neglect and impairments of spatial analysis and visual perception. *Brain*, **97**, 551–564.

PANDYA, D. N., KAROL, E. A. and HEILBRONN, D. (1971) The topographical distribution of interhemispheric projections in the corpus callosum of the rhesus monkey. *Brain Research, Amsterdam*, **32**, 31–43.

—— and KUYPERS, H. G. J. M. (1969) Cortico-cortical connections in the rhesus monkey. *Brain Research, Amsterdam*, **13**, 13–36.

—— and VIGNOLO, L. A. (1968) Interhemispheric neocortical projections of somatosensory areas I and II in the rhesus monkey. *Brain Research, Amsterdam*, **7**, 300–303.

—— —— (1969) Interhemispheric projections of the parietal lobe in rhesus monkey. *Brain Research, Amsterdam*, **15**, 49–65.

SCHWARTZ, A. S., MARCHOK, P. L. and FLYNN, R. E. (1977) A sensitive test for tactile extinction: results in patients with parietal and frontal lobe disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 228–233.

SEMMES, J. (1968) Hemispheric specialization: A possible clue to mechanism. *Neuropsychologia*, **6**, 11–26.

SHAPIRO, M. F. and FELDMAN, D. S. (1952) Double simultaneous stimulation phenomena in spinal cord disease. *Neurology, Minneapolis*, **2**, 509–513.

SPARKS, R. and GESCHWIND, N. (1968) Dichotic listening in man after section of the neocortical commissures. *Cortex*, **4**, 3–16.

—— GOODGLASS, H. and NICHEL, B. (1970) Ipsilateral *vs* contralateral extinction in dichotic listening resulting from hemisphere lesions. *Cortex*, **6**, 249–260.

SPRINGER, S. P. and GAZZANIGA, M. S. (1975) Dichotic testing of partial and complete split-brain subjects. *Neuropsychologia*, **13**, 341–346.

TENG, E. L. and SPERRY, R. W. (1973) Interhemispheric interaction during simultaneous bilateral presentation of letters or digits in commissurotomized patients. *Neuropsychologia*, **11**, 131–140.

WATSON, R. T., HEILMAN, K. M., CAUTHEN, J. C. and KING, F. A. (1973) Neglect after cingulectomy. *Neurology, Minneapolis*, **23**, 1003–1007.

WELMAN, A. J. (1969) Right-sided unilateral visual spatial agnosia, asomatognosia, and anosognosia with left-hemisphere lesions. *Brain*, **92**, 572–582.

ZARIT, S. H. and KAHN, R. L. (1974) Impairment and adaption in chronic disabilities: spatial inattention. *Journal of Nervous and Mental Disease*, **159**, 63–72.

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CONSTANT ERROR OF VISUAL EGOCENTRIC ORIENTATION IN PATIENTS WITH ACUTE VESTIBULAR DISORDER

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INTRODUCTION

VISUAL projection in space is peripherally based upon the possession by each retinal receptor of 'local sign', a term originally introduced by Helmholtz (1910). Local sign is pre-eminently a function of the fovea which forms the primary point of directional reference. Images falling on the fovea are projected upon a line passing through the nodal point of the eye, constituting the line of 'principal visual direction' (*see* Duke-Elder, 1973). In binocular vision, corresponding retinal points have identical local sign values and the two eyes appear to act as a single, centrally-situated 'cyclopean eye' (Hering, 1861). According to Hering's law of cyclopean projection, superimposed images formed on the fovea have identical 'oculocentric direction'. To localize an object in space, however, information is also needed about position of the eyes and the fovea in relation to the head and body, which means that spatial judgements must be complemented by some kind of extraretinal information. The perceptual counterpart of oculocentric direction is the 'egocentric direction' (Roelofs, 1959), which is judged with reference to co-ordinates of the head and body. Bi-directional judgements of visual objects in space, such as 'straight ahead, to the left or to the right', etc. are made in relation to the egocentre, which is fixed in relation to the body and situated in the median plane of the head (*see* Howard and Templeton, 1966). The line of principal visual direction normally corresponds to the perceptual concept of 'straight ahead'.

The ultimate, visual, directional orientation depends upon the central processing and synthesizing at a perceptual level of retinal inflow and extraretinal factors related to postural activity of the body and the head and notably to the activity of the extraocular muscles. Disturbances of any of these systems may result in an illusory perception of false visual projection.

The aim of the present paper is to present the effects upon directional, visual judgements of an acute, unilateral, vestibular disorder. The problem more specifically concerns the effects of an asymmetric, vestibular inflow upon ocular position and the correlation between eye position and subjective visual space perception.

This is really part of a question which has attracted much interest in the past amongst psychologists, physiologists and clinicians: how do we perceive a spatially stable visual world?

Two theories have been proposed to explain extraretinal, oculomuscular influences upon visual space perception. One principal line of thought, originally presented by Helmholtz (1910), states that perception of space is based upon a central calculation of the motor 'outflow' to the extraocular muscles. In other words, correct localization in space depends upon the relation between intended and effected eye movements on the one hand and retinal projection on the other. This view has been supported by many authors, for instance, Bielschowsky (1935), Brindley and Merton (1960) and Festinger and Canon (1965). The second theory is based upon the supposition that space perception depends on proprioceptive 'inflow' from the extraocular muscles. The foremost advocate of this opinion was Sherrington (1918), later on followed by others (Tschermak-Seysenegg, 1947; Oppel, 1967). For a review of these and related problems *see* Gregory (1958) and Merton (1964).

MATERIAL

Normal Subjects

Twenty-five subjects aged between 20 and 56 years were examined for resting eye position in darkness and for direction of the visual 'straight ahead' with and without a visual frame of reference. The subjects were chosen at random amongst the staff at the Söder Hospital, Stockholm. The following criteria for normality were used; absence of any otological disease or episodes of vertigo, no history of nervous system disorders, no gross defects of visual acuity, no defects of the visual fields and no primary disturbance of ocular motility.

Patients

Fifteen patients with clinical signs pointing to an acute disorder of the peripheral vestibular system ('vestibular neuronitis') were examined for resting eye position in darkness and thereafter asked for visual directional judgements during simultaneous control of eye position in darkness. The patients were examined from one to four days after onset of the vertiginous symptoms. Six patients were female, 9 patients were male aged between 22 and 64 years. There were no limitations of range of pursuit or command eye movements tested in light. Neurological examination was normal except for the signs associated with the acute vestibular disorder.

METHODS

The subjects were all examined in the supine position. A special stand was mounted on a bed for support and fixation of the head. Above the head was mounted a metallic projection arc, on which the fixation target was presented. The arc had a radius of curvation of 30 cm. The subject's head and eyes were in the centre of the arc, which was graded in 5 degree intervals with zero corresponding to the median plane of the head. The stand also supported an infra-red television camera and four infra-red, solid-state lamps. Eye movements and eye positions were monitored on an ordinary television screen. (For details of the television equipment, *see* Hörnsten, Högman and Örnberg, 1973). The television method, of course, allowed inspection in ordinary visible light as well as in darkness. For observations in darkness the subject, the projection arc and the camera system were enclosed in a black box to exclude visual cues caused by light from the monitor screen.

For evaluation of the extent of ocular deviation in darkness, individual calibrations were made by having the subject direct his gaze towards the graduations on the arc subtending different visual angles. Deviations could then be marked by a pen on the monitor screen. Stability of head position in relation to the recording camera system was checked by marking the position of the median plane of the head on the monitor screen.

The fixation object in darkness was a small, self-luminous spot with a diameter of 4 mm. The spot was painted in a fluorescent colour on a small magnetic cylinder, which was moved on the projection arc by the experimenter and could be attached to the arc at any point. In a second set of experiments, a foveal after-image was used, together with the image of the real object. The after-image was a small cross produced by an electronic flashlight whilst the subject fixed his gaze on the centre of the figure.

PROCEDURE

1. *With Visual Frame*

The subjects had to indicate when a fixation point of the same magnitude as the spot used in darkness was perceived in the straight-ahead position on the projection arc (scale markings on the back of the arc). The fixation object was moved on the arc from the periphery of the visual field towards the median plane. The object was moved alternately from the left and right periphery and ten trials in total were made for each direction.

2. *Darkness*

(*a*) *Moving object; voluntary gaze deviations.* In this trial, which was performed only on normal subjects, the straight-ahead position of the spot had to be judged by the same procedure as described with visual frame, whilst the subjects voluntarily gazed to either side approximately 10 and 20 degrees, respectively.

(*b*) *Moving object; with and without after-image.* After determination of the resting position of the eyes in complete darkness the subjects were requested to judge when the moving luminous spot appeared in the straight-ahead position. The object was moved on the arc in the same way as described above, whilst the subjects were instructed to relax and look straight ahead. Thereafter the same procedure was repeated with the simultaneous presence of a real image (luminous spot) and an after-image.

(*c*) *Fixed object; with and without after-image.* In this trial, the luminous spot was placed in the objective median plane at the zero position of the arc whilst the subjects kept their eyes closed. Immediately after eye-opening (eyes deviated or non-deviated), they had to judge the direction of the spot in relation to the median plane. Then the subjects were instructed to gaze voluntarily from any deviated position until the eyes reached the primary position and then again report the apparent visual direction of the luminous point. As in the foregoing trial, the procedure was thereafter repeated with a simultaneous after-image.

Comment

Some comments concerning the exactness of the experimental situation in darkness are required. In situation 2, there were sporadic tendencies for the subjects to direct the eye towards the moving object. Such trials were excluded. The experimental situation allowed quantitative evaluation of steady ocular position within 2 to 3 degrees. In situation 2(*c*), only two kinds of qualitative reports were possible; judgements of the relative positions of the real image and the after-image and the position of both the images in relation to the visual egocentre.

The head fixation device did not completely exclude the possibility of very small head movements. It was, however, for practical reasons not convenient to use a bite-board for the patients with an acute vestibular disorder. The presence of significant head movements could be excluded by the checking procedure described above.

In all patients there was spontaneous nystagmus to a varying degree, which was the foremost obstacle to an exact evaluation of ocular position. Nystagmus, however, was beating within a rather limited range, not exceeding 2 to 4 degrees, and the average eye position could be reliably estimated by the markings on the monitor screen. The error introduced by spontaneous nystagmus is inherent in the experimental/pathological condition. The nystagmus in most cases was accompanied by some oscillopsia, which could render precise judgements of target localization difficult for the patients. Significant disturbances introduced by autokinetic sensations did not appear in the trials.

All methodological limitations considered, the most serious of which were inherent to the pathological condition, it can be stated that the recording inaccuracies were small compared to the high degree of ocular deviations.

RESULTS

Normal subjects

With access to a visual frame of reference, the straight-ahead judgements always coincided with the objective median plane. In darkness, a slight tendency to a horizontal eye deviation, of less than 5 degrees, was observed in 6 subjects. For the remainder, no appreciable deviation of the resting position of the eyes in darkness was noted.

When a fixation point was introduced in darkness, no lateral displacement of the eyes occurred and the straight-ahead judgements always corresponded to the median plane within a range not exceeding 2 to 3 degrees. No consistent difference could be noted between those subjects who exhibited small lateral deviations of the resting eye position and the rest of the normal subjects. Absence of such errors could be explained by the limitations of exactness of the measuring procedure. Voluntary lateral eye deviations did not alter the relation between judged straight ahead and the objective median plane within the same limits of error as described above.

Patients

1. *Visual frame of reference.* With a visual frame of reference, all patients accurately judged the visual straight ahead as aligned with the objective median plane. That is, oculocentric and egocentric visual directions coincided.

2. *Darkness.* All patients disclosed quite marked horizontal, continuous eye deviations of constant amplitude in the absence of a visual frame of reference. The deviations ranged from approximately 10 to 25 degrees. Spontaneous nystagmus was in all cases beating in the opposite direction to ocular deviation. (Where oscillopsia was present, a more or less distinct sensation of a 'streaming' motion of the target towards the fast phase of nystagmus was reported.)

With the eyes in the resting, deviated position 2(*b*), the perception of the subjective straight ahead was in all cases displaced towards the side of ocular deviation to an extent which closely corresponded to ocular position (*see* fig. 1). When an after-image was introduced, the real image and the after-image were superimposed.

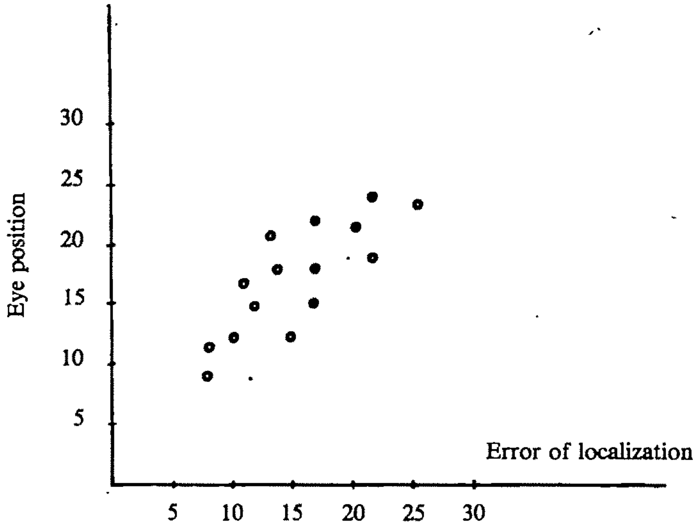

FIG. 1. Degrees of ocular rest position in darkness and error of visual straight-ahead localization. Arithmetic means of twenty trials for each patient.

With the eyes in the resting, deviated position and the fixed spot presented in the objective median plane 2(*c*), all patients, after eye opening, judged the spot to be dislocated far to the side opposite to the direction of ocular deviation (for example, with ocular deviation to the right, the spot was displaced to the left). With simultaneous presentation of a real object and an after-image, there was a separation between the two images. The image of the real object (spot) was still judged as displaced, in the same direction and to approximately the same extent as before. The after-image, however, was judged to be straight ahead.

In the second part of trial 2(*c*) when the patients voluntarily moved their eyes to the median plane, the spot fixed at zero position still seemed to be displaced in a direction opposite to the basic resting deviation. Most patients judged the displacement to be of the same magnitude as in the first part of this trial. Some patients, however, seemed to experience an increased sensation of displacement. When the trial was repeated with a simultaneous after-image, the real image and the after-image were judged to be superimposed or situated very close to each other.

DISCUSSION

Disturbances of visual egocentric localization have been clinically recognized in patients with recent paresis of extraocular muscles for more than a century (von Graefe, 1854) and are a commonplace experience in clinical practice (*see* Cogan, 1966; Walsh and Hoyt, 1969).

A simple explanation of false visual egocentric localization (as indicated by past-pointing) with extraocular paresis could be given by referring to the abnormal retinal image projection caused by the failure of the eye to be accurately directed against the object of intended gaze. The extent of false localization then would be determined by the retinal image projection in relation to the fovea. Such a theory exclusively utilizes retinal local sign and has been supported by, amongst others, Adler (1945), Goswami (1967), Bedrossian (1969) and Walsh and Hoyt (1969). It has, however, been demonstrated that false orientation cannot be satisfactorily explained by retinal local sign alone, but is caused by the added effects of retinal image projection and extraretinal factors related to the extraocular muscles. In fact, this was realized by von Graefe (1854) who stated that past-pointing could not be due exclusively to retinal local sign, but was related to oculomuscular abnormality; 'the patient is given the impression that he has turned his eye much more than is in fact the case: which results in a dislocation of the visual field in relation to his body', a statement which illustrates the distinction of egocentric visual localization.

Experimental evidence of extraretinal influences upon visual egocentric localization has been offered after pharmacological paralysis of extraocular muscles (Kornmüller, 1931) or when ocular movements are mechanically restrained (Mach, 1886). Brindley and Merton (1960) performed related experiments and noted an apparent displacement of the visual world in the direction of intended gaze when the eyes were fixed by forceps and after partial paresis of extraocular muscles by administration of curare. They concluded that the perceptual errors could only be explained by the effort of will employed in attempts to move the eyes. The same kind of explanation for past-pointing in paralytic strabismus was proposed by von Noorden, Awaya and Romano (1970), who convincingly demonstrated that false orientation is caused by a disproportion between motor innervation and its effects.

Time-honoured observations of the perceptual consequences of passive and active eye movements may illustrate the role of the extraocular muscles. When the eyes are voluntarily moved, the visual world is stable. With passive eye movements, for instance, by pushing the eye with the finger, a movement of visual space is perceived in a direction opposite to the ocular displacement. Evidently, retinal image displacement may or may not cause a sensation of apparent movement and displacement of visual space. The perceptual divergence caused by active and passive eye movements was ascribed by Helmholtz (1910) to a central monitoring of oculomotor outflow; 'our judgements as to the direction of the visual axis are simply the result of the effort of will involved in trying to alter the adjustment of the eyes'. It was emphasized by MacKay (1958) that an attempt to move the eyes is accompanied by an expected displacement of the retinal image, which means that oculomotor signals and information of retinal image displacement cancel each other out in the calculation of visual space. With passive eye movements, there is no cancellation of the retinal image, hence an apparent displacement of visual space occurs.

On the other hand, an induced after-image will be immobile with passive eye movements because there is allowance for neither a central oculomotor command, nor for any displacement of the retinal image. With active eye movements, the behaviour of an after-image is quite different. The after-image seems to move whether the intended eye movement can be effected or not (Helmholtz, 1910; Jampolsky, 1970); there is no cancellation of the oculomotor signal by any retinal image displacement, which means that the retinal after-image changes its space value, corresponding to the impulse for the eye movement.

Although most psychophysical and clinical evidence seems to confirm the 'outflow theory', it has not been completely unchallenged.

Some experimental observations on a few subjects directly contradict the outflow theory. According to Siebeck and Frey (1953) and Siebeck (1953), no illusory movement appears with attempted gaze in a completely curarized subject. Similar experiments have recently been performed on one subject by Stevens, Emerson, Gerstein, Kallos, Neufeld and Rosenquist (1976) who, after orbital administration of curare, reported that with subparalytic doses, an apparent movement was perceived, whereas no movement appeared with paralytic doses. However, apparent spatial displacement, as indicated by past-pointing, was reported with partial as well as complete paresis of extraocular muscles. The authors commented upon the results of Siebeck and Frey and pointed out that the latter had not made the distinction between apparent movement and displacement. They concluded that perception of spatial localization depends upon a spatial system (separate from an independent pattern visual system responsible for perceptions associated with movement) operating by monitoring the oculomotor outflow. An additional recent report (Brindley, Goodwin, Kulikowski and Leighton, 1977) confirms in all essentials the findings of Stevens *et al.* (1976). According to these authors, the results 'strongly suggests that proprioceptive information can be used in correcting eye movements; but the argument is not compelling'. Indications have also been presented in favour of an afferent inflow mechanism utilized for eye position information. Skavenski (1972) and Skavenski, Haddad and Steinman (1972) investigated the relative contribution of inflow and outflow to the control of eye position and the perception of direction. They concluded that some non-visual, afferent information can be used for position control but perception of direction depends primarily upon the outflow to the extraocular muscles.

Thus recent research indicates that outflow and inflow may contribute differentially to ocular position control and to perception of movement and direction; for perception of direction the outflow mechanism seems undisputed.

The principle of a central monitoring of oculomotor outflow has been called 'efference copy' (von Holst and Mittelstaedt, 1950) or 'corollary discharge' (Sperry, 1950). Modern cybernetic models of oculomotor control systems include the operation of such a principle; in the functional control of the pursuit system (*see* Young, 1971), for retinal error correction in the saccadic system (Robinson,

1975) and in visuovestibular interaction to account for stability of the visual world during head movements (Raphan, Cohen and Matsuo, 1977, Robinson, 1977).

From a clinical point of view, the discussion of the relative influences of outflow and inflow in extraocular paresis is summarized by von Noorden (1975): 'There is currently no clinical evidence to indicate the significance of inflow in either complementing or counteracting the information provided by outflow in the control of eye position or the perception of direction.'

Beside investigations concerned with the effects of clinical and experimental paresis of extraocular muscles upon visual egocentric localization there are several studies of the influence of experimental, vestibular stimulation upon visual perception and orientation. Only a few papers, however, have more specifically been concerned with egocentric localization.

A fixation target presented in the objective median plane and rotating with the observer in darkness would appear to move in the direction of acceleration (fast phase of nystagmus). The apparent movement is called the oculogyral illusion and was originally explained by retinal image displacement during the slow phase of nystagmus (Graybiel and Hupp, 1946). Conclusive arguments against an explanation in terms of retinal image tracking are based upon the fact that the illusion may appear even in the absence of any ocular nystagmus or retinal tracking. The illusion is thus present in patients with oculomuscular paresis or complete ophthalmoplegia (which renders nystagmic reactions impossible), with a stabilized retinal image (van Dishoeck, Spoor and Nijhoff, 1954, Byford, 1963) and with an induced visual after-image (Whiteside, Greybiel and Niven, 1965).

During angular acceleration of healthy subjects an apparent static target-displacement has been reported in the direction of rotation (Fischer, 1928, Fischer and Kornmüller, 1931, Morant, 1959). The target must be adjusted in the direction opposite to acceleration (slow phase of nystagmus) to be perceived in the apparent median plane. Brecher, Brecher, Kommerell, Sauter and Sellerbeck (1972) were able to demonstrate a progressive deviation of the subjective straight ahead with increasing angular acceleration. According to other authors, however, there is only a transitory displacement of the fixation target during vestibular stimulation (Byford, 1963, Whiteside *et al.*, 1965).

According to Fischer and Kornmüller (1931) the deviation of the subjective straight ahead may be caused by a deviation of the eyes in direction of the slow phase of nystagmus. In those experiments, however, there were no recordings of eye movement or eye position. In this context the observations of Byford (1963) are of special interest. By means of a sensitive, photoelectric contact-lens device, a deflection of the eyes in direction of the slow phase of nystagmus was recorded during strong angular acceleration. Byford pointed out that the displacement of the apparent median plane could be correlated to eye position. The deflection was found to 'be in broad quantitative agreement with the subject's estimate of the initial angular difference between the primary visual axis and his fixation lamp'.

However, in one subject with an abducent palsy (incapable of eye movement in one direction) and in subjects with stabilized retinal images, the illusion was not accompanied by any static displacement of the target.

The apparent visual target movement and displacement of the oculogyral illusion has been explained by Whiteside *et al.* (1965) as an effect of the efferent oculomotor program of those muscles which are antagonistic to the slow phase of nystagmus. This kind of explanation presupposes the operation of an efference copy. The explanation holds true for real images as well as for after-images, whether the movement is effected or not: for example, whether or not the fast-phase efferent activity results in an eye movement or not, there is no retinal image displacement to be cancelled out with a real object (saccadic suppression) or with an after-image. The resulting illusory movement thus will be in the direction of fast-phase efferent activity.

False localization occurring with extraocular paresis may be said to represent the end point of a kinetic illusory perception, which is characterized by a strong feature of illusory movement during an attempted saccade. The efference copy suggests that the eye has been moved and the movement is expected to be cancelled by a corresponding displacement of the retinal image of a stationary object. Thus, allowance is made for an eye movement which has not been effected and which is consequently not accompanied by any displacement of the retinal image. This is subjectively interpreted as if the stationary object is moving with the eye, and is displaced in the direction of attempted gaze.

An analogous hypothesis may be proposed to explain the apparent displacement of the median plane which occurs with steady eye deviations (continuous deviation of constant amplitude) in a vestibular disorder. Subjectively, the patients are unaware of the strong conjugate eye deviation. The efference copy tells them that the eyes are in a position of rest or straight ahead (which means zero value for ocular position). A visual object, isolated from other visual references, must also be projected with a zero value, that is, in the fovea, to be perceived as straight ahead. When the target is presented in the objective median plane and the eyes are still in a deviated position, the retinal image of the target is projected outside the fovea towards the ocular deviation. According to the efference copy, the target will be subjectively displaced away from the direction of ocular deviation. A foveally induced after-image, however, is perceived as separated from the real target and subjectively as straight ahead, because eye position and retinal projection both have zero values.

If the eyes are voluntarily deviated to the objective median plane and the visual target is presented in the same plane, the real target will still be perceived as displaced in the same direction and to the same extent. The displacement occurs in spite of foveal projection of the real target, because the efference copy suggests that the eyes are deviated (for example, in a patient with a left-deviated resting position, the efference copy suggests a right ocular deviation when the target is objectively in the median plane). This is interpreted as if the real target is displaced in the direction of efferent activity—the resemblance with false localization in oculomuscular paresis is apparent. A foveally induced after-image is now subjectively displaced in the same direction and to the same extent as the real target and is approximately superimposed upon the real target. The efference copy suggests that the eyes are deviated when the after-image is on the fovea; thus it moves with the direction of gaze in exactly the same manner as an after-image normally behaves with change of voluntary gaze.

Conjugate, horizontal eye deviation (of which the patient is totally unaware) towards the side of the lesion is a prominent feature of the lateral medullary syndrome (Hagström, Hörnsten and Silfverskiöld, 1969; Hörnsten, 1974). Kommerell and Hoyt (1973) tested the visuospatial orientation in a patient with a left lateral medullary syndrome. The patient was asked to look at a dim flashlight presented in complete darkness and to indicate the position of the fixation light immediately after it had been turned off. Past-pointing occurred to the right and the authors ascribed the spatial mislocation to the patient's false interpretation of gaze direction. The spatial disorientation in this case is the same as was found with subjects in the second test situation of trial 2(*c*). The constant error of visuospatial localization in the trials presented in this paper must basically be related to the conjugate eye deviation and the patients' false interpretation of direction of gaze.

The perceptual consequence of the ocular deviation can be represented by a simple diagram (modified from Robinson, 1975), which includes the operation of an efference copy or extraretinal position signal in the control of saccadic eye movements (*see* fig. 2). According to Robinson information of initial eye position relative to the skull is needed for the calculation of goal-directed saccadic eye movements. This requires that retinal error (e) (difference between eye position in space (E) and target position in space (T)) is added to an efference copy to create an internal representation of target position into a head-co-ordinate reference frame. 'How this signal is extracted from the visual system and where and how the efference copy is used is entirely unknown at present, and is, of course, of intense interest to those concerned with the problem of how we perceive the spatial location of seen objects' (Robinson, 1975).

In the presented cases the efference copy told that the eyes in darkness were directed straight ahead in spite of a strong lateral deviation. It thus seems reasonable to assume that the efference copy signal is taken off before the vestibular bias is added as shown in the diagram. Consequently, the efference copy does not reflect the entire, final oculomotor outflow. It must come from some place more centrally situated (Robinson, personal communication, 1979). The final outcome will be that a continuous error is introduced to the outer feed-back loop E-T with a resulting constant error of eye position relative to the visual target. The magnitude of the error will be proportional to the pathological vestibular inflow defined as degrees of lateral deviation.

Besides the psychophysical and clinical approach to problems of visuospatial stabilization, some important neurophysiological results have been obtained during recent years by single-cell recordings. The classic investigations of Hubel and Wiesel (1968) have shown that striate neurons in the monkey have a very high specificity for different visual parameters, such as orientation and direction. In the context of the matter of stabilization of the visual world, Wurtz (1969*a*) investigated the responses of striate neurons in the monkey during rapid eye movements and compared the effects of eye movement and stimulus movement.

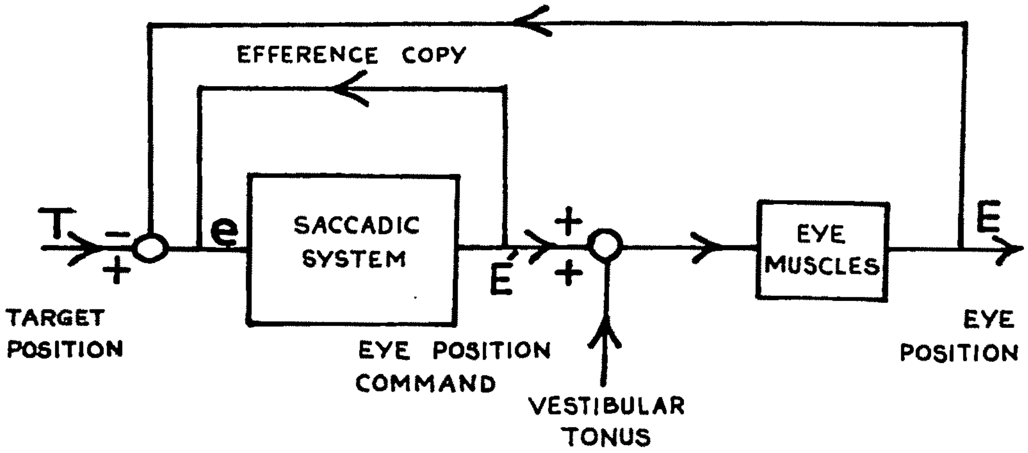

FIG. 2. Diagram showing the efference copy signal taken off before the vestibular bias.

He found that of a total sample of 188 neurons giving an excitatory response to a stationary or slowly moving stimulus when the eyes were still, about half did not respond at all during a rapid eye movement. During rapid eye movements some neurons reversed from an excitatory response to a stationary stimulus to a suppression response when the eye rapidly moved over the same stimulus. According to Wurtz, the suppression neurons may be well suited to signal rapid translation of the visual background and provide some information that a rapid eye movement has occurred. Those findings may indicate that cues for stability of the visual world are available in terms of striate response patterns. Wurtz (1969*b*) also considered the question whether absence of response in half of the 188 striate neurons during rapid eye movement could be explained by an active inhibition of a corollary discharge, by comparing the response during a rapid eye movement across a stationary stimulus with the response during rapid stimulus movement in front of a stationary eye. With a corollary discharge, a difference of the neural response would be expected depending on whether a retinal stimulus movement is caused by a real movement of the object or a movement of the eye. Wurtz did not find any evidence of a corollary discharge operating at the level of the striate cortex. The findings, however, did not exclude the possibility of a corollary discharge at other levels of the visual system. Such evidence was found by Robinson and Wurtz (1975) in neurons in the superficial layers of the monkey's superior colliculi which can differentiate between retinal stimulus movement induced by actual movement of an object and by eye movement. There is a striking suppression of activity in cells which responds to visual stimuli in association with eye movements. The suppression is present in light as well as in darkness and the inference is made that the suppression must result from an extraretinal signal with characteristics which would be expected by a corollary discharge although '. . . proprioception as a source of the extraretinal signal can not be excluded'.

According to Robinson and Wurtz (1975), information coded in the collicular cells may have a perceptual function via colliculo-thalamocortical projections. Execution of a goal-directed saccade presupposes coding of target position in space, that is, in a head-body frame of reference. This, as stated above, besides a retinal error signal, demands an extraretinal error signal, which may be conveyed by 'quasivisual' cells of the superior colliculi in the monkey (Sparks, Mays and Pollack, 1977). Those findings are compatible with Robinson's model (1975) of the saccadic system, in which the extraretinal signal (efference copy) is added to retinal error to provide an internal representation of target position with respect to the head.

Finally, there is some physiological evidence for interaction between oculomotor proprioception and the primary visual cortex in the cat. Fiorentini and Maffei (1977) have shown that interruption of extraocular proprioceptive inflow in the cat results in instability of ocular position and pendular oscillations in darkness, which may be an indication of the role of ocular proprioception for oculomotor function and visual stability.

To conclude with a quotation from a recent workshop summary of supranuclear influences upon brain-stem gaze neurons (Roucoux and Crommelinck, 1977) '. . . an efference copy would elegantly solve the problem of perceptual space stability. In this context, the role of proprioception remains mysterious'.

For the time being, we must accept the operation of an efference copy to explain the phenomenon of false visual localization. In the case of an extraocular muscle paresis, the copy comprises an intact prenuclear and nuclear gaze mechanism which does not result in an adequate motor response. In the case of an acute peripheral vestibular disorder, there are no primary oculomotor defects at prenuclear, nuclear or peripheral levels. The pontine centres for horizontal gaze, however, are unevenly loaded by the asymmetric vestibular inflow at a prenuclear oculomotor level, which results in a directionally constant distortion of the efference copy, and, at the perceptual level, results in a constant error of visuospatial localization.

SUMMARY

Errors of visual egocentric localization are well-known in patients with paresis of ocular muscles or paresis of conjugate gaze. In the present paper a series of patients with unilateral vestibular disorder disclosed a constant lateralization of the visual egocentre in the absence of any ocular paresis. The perceptual illusion is associated with an altered resting position of the eyes caused by the vestibular imbalance. The disturbance of visual, egocentric localization was revealed only after elimination of the visual frame of reference and the extent of lateralization of the visual egocentre was proportional to the degree of resting deviation of the eyes.

Although the findings are of limited clinical importance they have a considerable theoretical interest. From the clinical point of view they may provide a basis for further understanding of the complex perceptual illusions which may accompany disorders affecting central vestibulo-ocular connections.

The results indicate that the perceptual effects are related to an altered central evaluation of the oculomotor programme and thus depend upon the operation of an 'efference copy'. This hypothesis is discussed with reference to earlier and current theories of visual localization.

REFERENCES

ADLER, F. H. (1945) Pathological physiology of convergent strabismus. Motor aspects of the non-accommodational type. *Archives of Ophthalmology, Chicago*, **33**, 362–377.

BEDROSSIAN, E. H. (1969) *The Surgical and Nonsurgical Management of Strabismus*. Springfield, Illinois: Charles C. Thomas, p. 125.

BIELSCHOWSKY, A. (1935) Lectures on motor anomalies of the eyes. II. Paralysis of individual eye muscles. *Archives of Ophthalmology, Chicago*, **13**, 33–59.

BRECHER, G. A., BRECHER, M. H., KOMMERELL, G., SAUTER, F. A. and SELLERBECK, J. (1972) Relation of optical and labyrinthean orientation. *Optica Acta*, **19**, 467–471.

BRINDLEY, G. S., GOODWIN, G. M., KULIKOWSKI, J. J. and LEIGHTON, D. (1977) Stability of vision with a paralysed eye. *Journal of Physiology, London*, **258**, 65–66P.

—— and MERTON, P. A. (1960) The absence of position sense in human eye. *Journal of Physiology, London*, **153**, 127–130.

BYFORD, G. H. (1963) Eye movements and the optogyral illusion. *Aerospace Medicine*, **34**, 119–123.

COGAN, D. G. (1966) *Neurology of the Ocular Muscles*. Springfield, Illinois: Charles C. Thomas, p. 187.

DISHOECK, H. A. E. VAN, SPOOR, A. and NIJHOFF, P. (1954) The opto-gyral illusion and its relation to the nystagmus of the eyes. *Acta Otolaryngologica*, **44**, 599–607.

DUKE-ELDER, S. (1973) *System of Ophthalmology*, Vol. IV. The physiology of the eye and of vision. London: Henry Kimpton, p. 340.

FESTINGER, L. and CANON, L. K. (1965) Information about spatial location based on knowledge about efference. *Psychological Review*, **72**, 373–384.

FIORENTINI, A. and MAFFEI, L. (1977) Instability of the eye in the dark and proprioception. *Nature, London*, **269**, 330–331.

FISCHER, M. H. (1928) Die Regulationsfunktionen des menschlichen Labyrinths und die Zusammanhänge mit verwandten Funktionen. In: *Ergebnisse der Physiologie*. Edited by L. Asher and K. Spiro. München: Bergmann, pp. 243–254.

—— and KORNMÜLLER, A. E. (1931) Egozentrische Lokalisation. 2. Mitteilung (optische Richtungslokalisation beim vestibulären Nystagmus). *Journal für Psychologie und Neurologie, Leipzig*, **41**, 383–420.

GOSWAMI, A. P. (1967) A theory for false projection. *Acta Ophthalmologica*, **45**, 699–702.

GRAEFE, A. VON (1854) Beiträge zür Physiologie und Pathologie der schiefen Augenmuskeln. *Albrecht von Graefes Archiv für Ophthalmologie*, **1**, 1–81.

GRAYBIEL, A. and HUPP, D. I. (1946) The oculo-gyral illusion: A form of apparent motion which may be observed following stimulation of semicircular canals. *Journal of Aviation Medicine*, **17**, 3-27.

GREGORY, R. L. (1958) Eye movements and the stability of the visual world. *Nature, London*, **182**, 1214-1216.

HAGSTRÖM, L., HÖRNSTEN, G. and SILFVERSKIÖLD, B. P. (1969) Oculostatic and visual phenomena occurring in association with Wallenberg's syndrome. *Acta Neurologica Scandinavica*, **45**, 568-582.

HELMHOLTZ, H. VON (1910) *Handbuch der Physiologischen Optik*. Dritter Band. 3rd edition. Hamburg and Leipzig: Voss, pp. 129-226.

HERING, E. (1861) *Beiträge zur Physiologie*. Leipzig: Engelmann, Heft 1, pp. 35-64.

HOLST, E. VON and MITTELSTAEDT, H. (1950) Das Reafferenzprinzip. *Naturwissenschaften*, **37**, 464-476.

HÖRNSTEN, G. (1974) Wallenberg's syndrome. Part II. Oculomotor and oculostatic disturbances. *Acta Neurologica Scandinavica*, **50**, 447-468.

—— HÖGMAN, B. and ÖRNBERG, G. (1973) Infrared methods for studying nystagmus and eye deviations in complete darkness with special reference to vertical nystagmus. *Acta Neurologica Scandinavica*, **49**, 511-524.

HOWARD, I. P. and TEMPLETON, W. B. (1966) *Human Spatial Orientation*. London, New York, Sidney: John Wiley, pp. 12-20.

HUBEL, D. H. and WIESEL, T. N. (1968) Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, London*, **195**, 215-243.

JAMPOLSKY, A. (1970) Ocular divergence mechanisms. *Transactions of the American Ophthalmological Society*, **68**, 772-782.

KOMMERELL, G. and HOYT, W. F. (1973) Lateropulsion of saccadic eye movements. *Archives of Neurology, Chicago*, **28**, 313-318.

KORNMÜLLER, A. E. (1931) Eine experimentelle Anästhesie der äusseren Augenmuskeln am Menschen und ihre Auswirkungen. *Journal für Psychologie und Neurologie*, **41**, 354-366.

MACH, E. (1886) Beiträge zur Analyse der Empfindungen. Jena: Fischer. *The Analysis of Sensations*. English translation by C. M. Williams (1959). New York: Dover Publications, p. 128.

MACKAY, D. M. (1958) Perceptual stability of a stroboscopically lit visual field containing self-luminous objects. *Nature, London*, **181**, 507-508.

MERTON, P. A. (1964) Absence of conscious position sense in the human eyes. In: *The Oculomotor System*. Edited by M. B. Bender. New York and London: Harper and Row, pp. 314-320.

MORANT, R. B. (1959) The visual perception of the median plane as influenced by labyrinthian stimulation. *Journal of Psychology*, **47**, 25-35.

NOORDEN, G. K. VON (1975) Oculomotor effect on vision—clinical aspects. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Edited by G. Lennerstrand and Paul Bach-y-Rita. Oxford. New York and Toronto: Pergamon Press, pp. 417-425.

—— AWAYA, S. and ROMANO, P. E. (1970) Past-pointing in paralytic strabismus. *Transactions of the American Ophthalmological Society*, **68**, 72-85.

OPPEL, O. (1967) Über die motorischen, sensorischen und sensiblen Nerveneinrichtungen im menschlichen Augenmuskelapparat und ihre sinnesphysiologische Bedertung. *Albrecht von Graefes Archiv für Ophthalmologie*, **171**, 337-366.

RAPHAN, T., COHEN, B. and MATSUO, V. (1977) A velocity-storage mechanism responsible for optokinetic nystagmus (OKN), optokinetic after-nystagmus (OKAN) and vestibular nystagmus. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 37–47.

ROBINSON, D. A. (1975) Oculomotor control signals. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Edited by G. Lennerstrand and Paul Bach-y-Rita. Oxford, New York and Toronto: Pergamon Press, pp. 337-378.

—— (1977) Vestibular and optokinetic symbiosis: An example of explaining by modelling. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 49-58.

ROBINSON, D. L. and WURTZ, R. H. (1975) Use of an extraretinal signal by monkey superior colliculus neurons to distinguish real from self-induced stimulus movement. *Journal of Neurophysiology*, **39**, 852–870.

ROELOFS, C. O. (1959) Considerations on the visual egocentre. *Acta Psychologica*, **16**, 226–234.

ROUCOUX, A. and CROMMELINCK, M. (1977) Influence of supranuclear structures on brain stem neurons B: collicular, thalamic and cortical influence on brain stem neurons. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 483–488.

SHERRINGTON, C. S. (1918) Observations on the sensual role of the proprioceptive nerve-supply of the extrinsic ocular muscles. *Brain*, **41**, 332-343.

SIEBECK, R. (1953) Wahrnehmungsformen bei experimentellen Augenmuskellähmungen. *Bericht über die Zusammenkunft der deutschen ophthalmologischen Gesellschaft*, **58**, 24–27.

—— and FREY, R. (1953) Die Wirkkungen Muskelerschlaffender Mittel auf die Augenmuskeln. *Der Anaesthetist*, **2**, 138-141.

SKAVENSKI, A. A. (1972) Inflow as a source of extraretinal eye position information. *Vision Research*, **12**, 221-229.

—— HADDAD, G. and STEINMAN, R. M. (1972) The extraretinal signal for the visual perception of direction. *Perception and Psychophysics*, **11**, 287-290.

SPARKS, D. L., MAYS, L. E. and POLLACK, J. G. (1977) Saccade-related unit activity in the monkey superior colliculus. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 437–444.

SPERRY, R. W. (1950) Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of Comparative and Physiological Psychology*, **43**, 482–489.

STEVENS, J. K., EMERSON, R. C., GERSTEIN, G. L., KALLOS, T., NEUFELD, G. R., NICHOLS, C. W. and ROSENQUIST, A. C. (1976) Paralysis of the awake human: visual perceptions. *Vision Research*, **16**, 93-98.

TSCHERMAK-SEYSENEGG, A. VON (1947) *Einführung in die physiologischen Optik*. Wien: Springer, pp. 140-145.

WALSH, F. B. and HOYT, W. F. (1969) *Clinical Neuro-ophthalmology*. Baltimore: Williams and Wilkins, pp. 147–148.

WHITESIDE, T. C. D., GRAYBIEL, A. and NIVEN, J. I. (1965) Visual illusions of movement. *Brain*, **88**, 193–210.

WURTZ, R. H. (1969*a*) Response of striate cortex neurons to stimuli during rapid eye movements in the monkey. *Journal of Neurophysiology*, **32**, 975–986.

—— (1969*b*) Comparison of effects of eye movements and stimulus movements on striate cortex neurons of the monkey. *Journal of Neurophysiology*, **32**, 987–994.

YOUNG, L. R. (1971) Pursuit eye tracking movements. In: *Control of Eye Movements*. Edited by P. Bach-y-Rita, C. C. Collins and J. E. Hyde. New York and London: Academic Press, pp. 429–442.

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Brain (1979), **102**, 701-725

ULTRASTRUCTURAL CHANGES IN POLYMYOSITIS

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INTRODUCTION

MANY reports on the ultrastructural changes in polymyositis have revealed a wide variety of alterations. In an endeavour to obtain the whole spectrum of the changes and the frequency with which they occur, a large series of cases of polymyositis has been investigated.

MATERIAL AND METHODS

Muscle biopsies obtained from 30 cases with polymyositis and 2 with dermatomyositis (Cases 27 and 29) were studied. These cases were selected from patients who were diagnosed clinically as having these disorders and who also showed histological evidence of inflammatory myopathy. Thirty of the patients were investigated at the National Hospitals, Queen Square and Maida Vale from 1965 to 1978. One was a patient in the Italian Hospital in Queen Square and another in the Royal Surrey County Hospital. Cases of collagen diseases were included only when the muscle weakness was a main symptom. The histological diagnosis was made by light microscopy using frozen, paraffin and plastic embedded sections. Cases with the histological features of polyarteritis nodosa or granulomatous myopathy were excluded.

The cases with polymyositis included 24 cases (1-24) without evidence of other disorders and 6 cases associated with other conditions. The latter consisted of 2 cases with fibrosing alveolitis (26 and 28), one with rheumatoid arthritis (Case 25), one with Sjögren's syndrome (Case 30) and 2 with carcinoma (Cases 31 and 32). The cases of polymyositis included 21 females and 9 males. The ages ranged from 11 to 72 years. Their average age was 49 years. The duration of their muscle symptoms ranged from one month to twelve years, their average duration being 3.1 years. Both patients with dermatomyositis were males in their forties. Steroid therapy had already been started at the time of the muscle biopsy in three cases of polymyositis and a case of dermatomyositis. A summary of the clinical findings was given by Matsubara (1978).

The biopsies were taken under either local or general anæsthesia. To avoid undue contraction of the muscle, the specimen was taken using an isometric clamp and placed immediately in 3 per cent glutaraldehyde in Sørensen's phosphate buffer at pH 7.4 at 4° C and fixed for two hours. The specimen was then released from the clamps, cut into pieces about 3 × 1.5 mm and post-fixed in 1 per cent osmium tetroxide in Michaeli's Veronal acetate buffer at pH 7.4. The tissue was then washed in water and dehydrated in ascending grades of alcohol and embedded in Epon 812 mixture. After

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TABLE. DATA OF 32 CASES

Case	*Sex*	*Age (yrs)*	*Duration symptoms pre-hosp.*	*Muscles first involved*	*Tendon reflexes*	*WCB/ (mm³)*	*ESR 1st h (mm)*	*CPK IU/l*	*Anti-N anti-body*	*RA test*	*EMG*	*Treatment*	*Result*
1	M	40	7 w	Shoulders, arms, trunk	Depressed in arms	7500	4	1070	+		F, MC	Prednisolone	Improved
2	F	20	9 w	Thighs, shoulders	Present	7800	2	1380	—		F, psw, P, FIP	Prednisolone	Improved
3	F	11	3 m	Limbs, trunk, facial	TJs, SJs absent, others depressed	5400	13	1825			F, b,P, FIP	Prednisolone	
4	F	21	3 m	Proximal muscles limbs	All present	6900	15	2132		—	F, b,P, FIP	Steroids	
5	M	72	3.5 m	Proximal muscles limbs	AJs absent. KJs sluggish	10 900	27	3200	—		F, b,P, RIP	Prednisolone	Improved
6	F	60	3.5 m	Legs then all muscles	All depressed	18 000	104	1113	—		F, P, FIP	Steroids, later cyclophosphamide	Improved
7	F	63	6 m	Proximal muscles limbs	All present	8000	4	2650	+	+	MC	—	Died
8	F	28	11 m	Proximal muscles limbs	Present and equal	6200	13	1000	—		MC	Prednisolone	
9	M	58	19 m	Legs and arms	Absent except AJs	13 700	7	363			F, b,P, FIP	Steroids, azathioprine	Improved
10	M	16	3 y	Legs, arms, shoulders	Flicker in arms, KJs, AJs present			9050			F	Steroids	Improved
11	F	55	2.5 y	Legs then arms	Present and equal	4500	14	158	+		b,P, RIP	Prednisolone	Improved then deteriorated
12	F	20	3 y	Legs then arms	TJs absent, others present	normal	normal	normal			F	Steroids	
13	M	54	3 y	Legs	Present and equal	5200	1	182			F, laP, RIP	Prednisolone	
14	F	36	4 y	Legs and arms	R. KJ depressed, others present	13 000	11	275	—		b,P	Steroids	Improved
15	M	47	4 y	Legs and arms	Present and equal	5300	9	136		—	F, blaP	Prednisolone	
16	F	54	2 y	Proximal muscles legs	Present and equal	6500	13	95	+		sp, FIP	Prednisolone	No improvement
17	M	57	4 y	Legs then arms	TJs, KJs absent, others present			109			b, laP	Steroids, methotrexate	No improvement
18	F	69	4 y	Legs	Only BJs and TJs elicited						b,P	ACTH	Improved
19	M	58	6 y	Proximal muscles limbs	BJs, SJs absent, others depressed	8300	2	63			ldP	Prednisolone, azathioprine	Improved
20	F	67	7 y	Proximal muscles legs	Present and equal	2500	87	32.8	+	+	b,P	Steroids	Definite improvement
21	F	61	8 y	Proximal muscles legs	Absent	11 000	34	20			MC	Steroids	No improvement
22	M	28	10 y	All limbs	All depressed			1810			MC	Prednisolone	No improvement
23	F	46	11 y	Proximal muscles, trunk	Absent	3500	14	717	+	—	blaP	Steroids	No improvement
24	F	67	12 y	Leg muscles	BJs and KJs hypo-active	9700	12	33 7			b,P	Steroids	No improvement

25	F	60	1 m	Neck, arms, legs	Present and equal			326		+	MC	Steroids	Muscles improved but died of perforated gastric ulcer
26	F	63	1 y	Proximal muscles	Present and equal	14 800	35	5	—	—	b,P, FIP	Prednisone	Initially improved
27	M	49	8 m	Proximal muscles	Present and equal	11 300	5	59			normal	Steroids	Improved
28	F	62	10 m	All limbs	Present and equal	7400	30	1230			F, giant P, RIP	Steroids	Relapsed
29	M	48	2 y	All limbs	Present and equal		35	250	+		F, MC	Prednisolone	No improvement
30	M	53	3 y	Legs, then all limbs	Present and equal	8000	63	470	+	+	MC	Prednisolone	
31	F	45	2 m	Swallowing, speaking, limbs	Present but depressed in arms						b, laP, P	Prednisolone	Responded well
32	F	66	4 m	Upper limbs	Present and equal	9400	101	910			F, P, RIP	Prednisolone	

Cases 2, 8, 9, 13 and 32 had pain as a presenting symptom. Cases 4, 14, 20 and 30 had symptoms of Raynaud's Syndrome. Cases 18 and 20 had impaired vibration sense in the legs. Cases 27 and 29 had dermatomyositis. Cases 26 and 28 had fibrosing alveolitis. Case 30 had Sjögren's syndrome. Case 25 had rheumatoid arthritis. Cases 31 and 32 had carcinoma of the breast and bronchus, respectively

Cases 4 and 6 were examined for LE cells with negative results

AJ = ankle jerk; BJ = biceps jerk; KJ = knee jerk; SJ = supinator jerk; TJ = triceps jerk; + = positive; — = negative.

EMG abbreviations

b = Brief
F = fibrillation potentials
FIP = full interference pattern
la = low amplitude potentials
ld = long duration potentials
MC = myopathic changes
P = polyphasic unit potentials
psw = positive sharp waves
RIP = reduced interference pattern
sp = spiky potentials

polymerization, overnight at 60° C, several sections 1 μm thick were cut from different blocks on an LKB ultramicrotome and stained with toluidine blue. After examination of the sections by the light microscope, portions of muscle were selected for thin-sectioning. Longitudinal and transverse sections of the muscle fibres were examined. On average, some four regions were chosen for sectioning; the thin sections, approximately 0.1 μm thick, were stained with uranyl acetate and then lead citrate. They were examined in a Siemens Elmiskop I.

OBSERVATIONS

By light microscopy all the biopsies showed damaged muscle fibres and obvious inflammatory changes. There was marked variation in the diameter of the muscle fibres. Some fibres were atrophied while others were hypertrophied. Individual fibres showed a wide variety of changes including hyaline and vacuolar degeneration; ring fibres occurred and some fibres were undergoing phagocytosis. Some fibres were basophilic suggestive of regeneration. Cellular infiltration of the interstitial tissue was present both around the blood vessels and between the muscle fibres. The interstitial tissue was increased in amount. Intramuscular nerves and muscle spindles were occasionally seen and usually appeared to be normal.

By electron microscopy, changes were seen both in the muscle fibres and interstitial tissue.

1. *Changes in the muscle fibres.* Most changes of the muscle fibres were non-specific and there was little difference between the cases of polymyositis with or without other disorders or in the cases of dermatomyositis.

The affected muscle fibres showed changes of the basement and plasma membranes, the contractile material, mitochondria, sarcoplasmic reticulum and T system and in the amount of ribosomes and glycogen granules. Structures present in the fibres included cytoplasmic bodies, concentric laminated bodies, honeycombs, rough endoplasmic reticulum, annulate lamellæ and thin and thick filamentous inclusions.

The surface of the muscle fibres was often indented. The basement membrane was occasionally multi-layered and in two cases was unusually thick. The plasma membrane was absent in some necrotic muscle fibres. The nuclei were often large and sometimes occurred in conglomerates. Nucleoli and nuclear bodies were commonly conspicuous.

There was often a marked variation in the degree of damage to adjacent muscle fibres. While some fibres showed marked change, adjacent fibres showed only minimal change (fig. 1). In the damaged fibres loss of myofilaments was frequent and often associated with changes of the Z line such as streaming and the formation of rods. Rods of Z line material were seen in 17 of the 32 cases and double Z lines in one case. Generally the thin myofilaments appeared to be more markedly damaged than the thick filaments, but in one case, some of the muscle fibres showed selective loss of the thick filaments. Cytoplasmic bodies were seen in 2 cases. Both ring fibres and sarcoplasmic masses were seen in the same muscle in

2 cases. Sarcoplasmic masses unaccompanied by ring fibres were seen in another case.

The mitochondria were often increased in number and showed marked variation in size and shape. Crystalline mitochondrial inclusions were noted in one of the cases. Concentric laminated bodies were present in some mitochondria in 2 cases.

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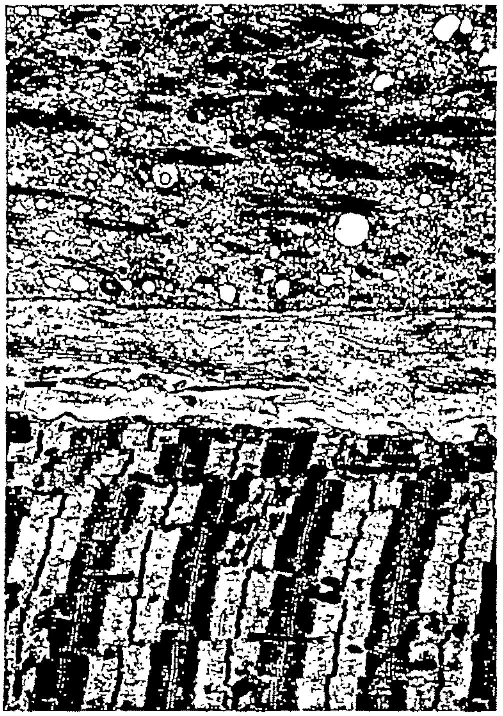

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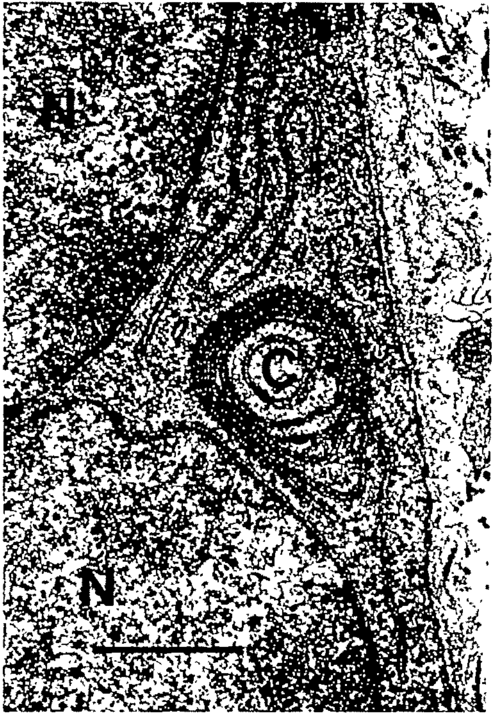
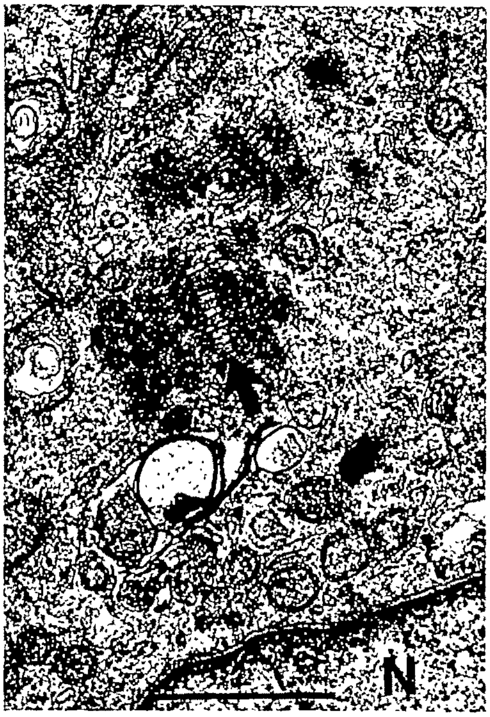


Fig. 1. Adjacent muscle fibres showed a marked contrast in the degree of structural change. The upper fibre showed severe loss of myofibrils and vacuolation while the lower fibre appeared relatively undamaged. (Female, 66, polymyositis with carcinoma of the bronchus, right biceps). Bar = 1.0 μm.

Fig. 2. Rough endoplasmic reticulum lay near two nuclei (N) of a muscle fibre which contained mature myofibrils. A portion of the endoplasmic reticulum assumed a concentric formation (C). (Female, 62, polymyositis with fibrosing alveolitis, left triceps). Bar = 1.0 μm.

The transverse tubular systems (T systems) commonly appeared to be increased in number and were elongated and dilated. Honeycombs which are derived from the T system were seen in 18 of the 32 cases. The lateral sacs of the sarcoplasmic reticulum were often distended and increased in number. The increased number of the lateral sacs and the T systems resulted in trains of these two structures which alternated with each other. In 3 cases of polymyositis, rough endoplasmic reticulum was seen in the perinuclear region of apparently mature muscle fibres. Some of the rough endoplasmic reticulum was concentrically disposed (fig. 2).

Annulate lamellæ were present in apparently mature muscle fibres in 2 cases (fig. 3). They were usually situated in the vicinity of the nuclei of the muscle fibres. They consisted of rows of electron dense rings approximately 100 nm in diameter and layers of parallel membrane which extended between these rings. The interval between adjacent membranes was 40–50 nm; the length of the membranes between two rings was up to 180 nm.



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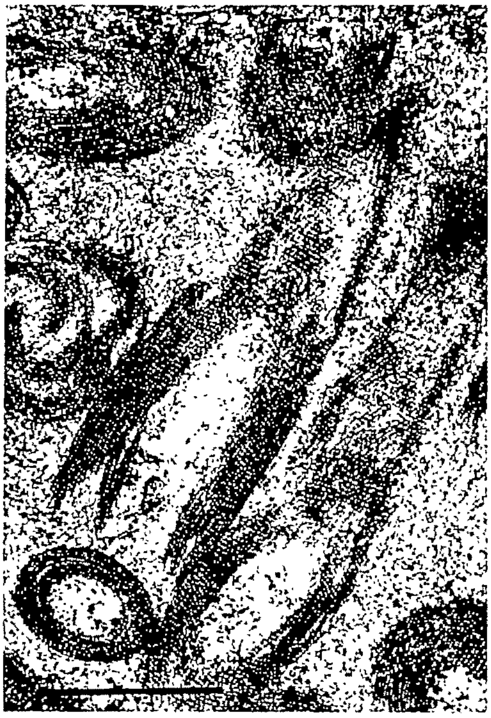

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FIG. 3. Annulate lamellæ near the nucleus (N) of a muscle fibre consisted of parallel rows of electron-dense rings or annuli between which extended thin parallel membranes (arrow). (Female, 61, polymyositis, left biceps). Bar = 1.0 μm.

FIG. 4. Cylindrical structures formed of concentric beaded laminæ occurred in the subsarcolemmal zone of some atrophied fibres in one of the cases of polymyositis. (Female, 36, polymyositis, left triceps). Bar = 1.0 μm.

In many muscle fibres, glycogen granules and lipid bodies in excessive amount were noted as well as numerous autophagic vacuoles, many of which contained myelin figures, glycogen granules and lipid bodies. Zebra bodies were seen in 2 cases and tubular aggregates were found infrequently in the muscle fibres in one case of the present series. Concentric laminated cylindrical structures with a beaded appearance (fig. 4) were observed in one of the cases.

Thin and thick filamentous inclusions were observed in the sarcoplasm and the nuclei of some muscle fibres. Bundles of thin filamentous inclusions about 2 nm

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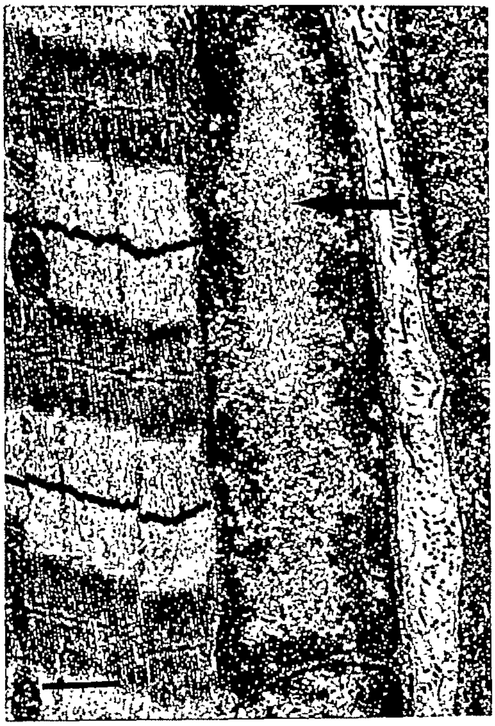

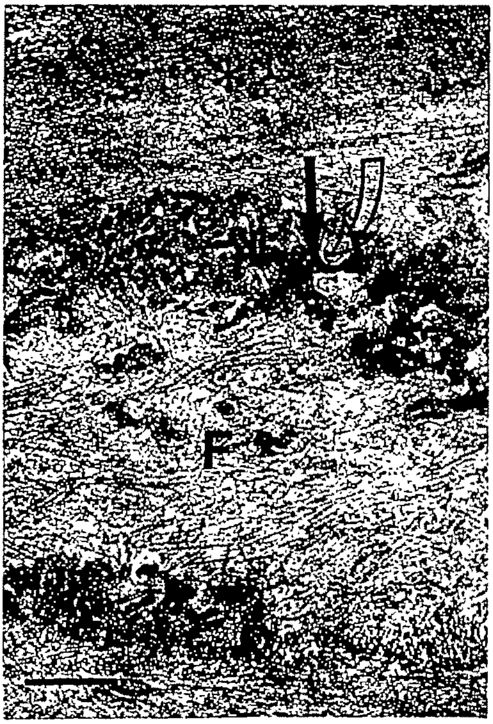

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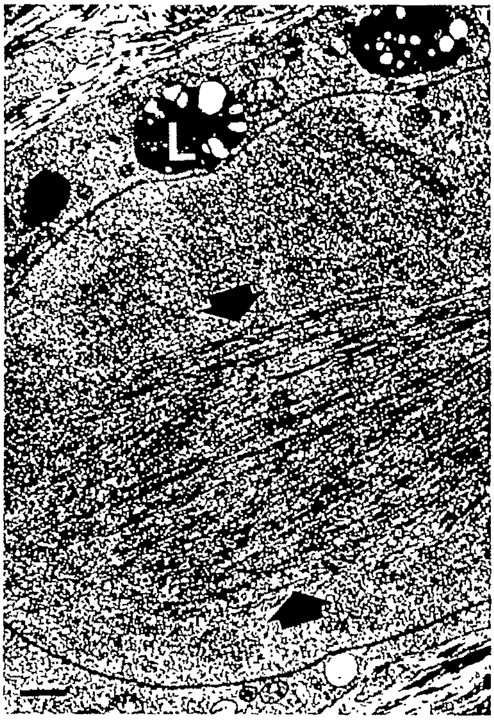
FIG. 5. Collections of thin filaments about 2 nm thick (arrow) were present in the nucleus of an otherwise normal looking muscle fibre in one of the cases of polymyositis. Similar filaments were also present in the sarcoplasm. (Female, 62, polymyositis with fibrosing alveolitis, left triceps). Bar = 1.0 μm.

FIG. 6. Fine filamentous material (*) surrounded coarse electron-dense strands (arrow) which were intermingled with tortuous tubules (open arrow) similar to the T system. These strands in turn surrounded a collection of thicker filamentous inclusions (F) about 15 nm in diameter. (Female, 61, polymyositis, left biceps). Bar = 1.0 μm.

thick were seen in the sarcoplasm and nuclei of a few muscle fibres in the case of polymyositis associated with fibrosing alveolitis (fig. 5). Thick filamentous sarcoplasmic inclusions approximately 15 nm thick were seen in the sarcoplasm of 3 cases of polymyositis unassociated with other disorder (fig. 6). All 3 had a chronic history of four to eight years. In one of the 3 cases, intranuclear filamentous inclusions of similar size and shape were also noted (fig. 7). The thick filamentous inclusions did not show cross striation; their length varied up to 1.0 μm. They usually occurred in muscle fibres showing disarray of the myofibrils, autophagic vacuoles, myelin figures, honeycombs and increased numbers of T systems and lateral sacs of the sarcoplasmic reticulum. Two of the 3 cases with thick filamentous inclusions also contained annulate lamellæ.

Satellite cells were frequent in most cases of polymyositis, particularly in young patients. Many of the satellite cells were rich in organelles such as ribosomes and mitochondria and often showed rough endoplasmic reticulum. Various stages of



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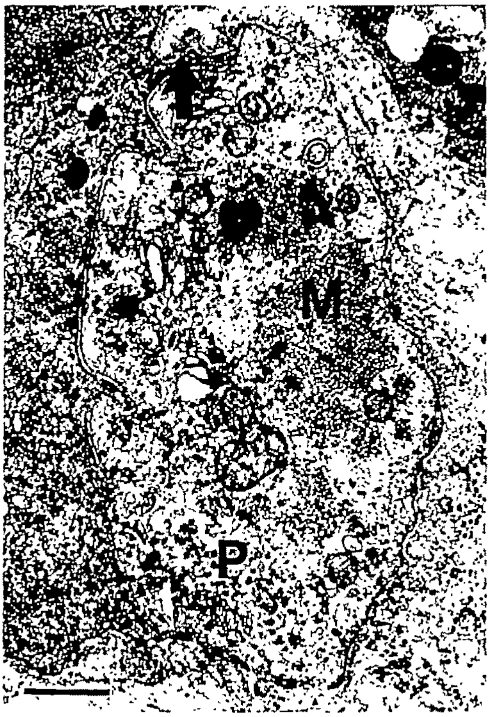

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FIG. 7. An abnormal muscle fibre, which presented lipid bodies (L) but little contractile material, had a large oval nucleus in which were bundles of filamentous inclusions (between arrows). The individual filaments were 15–20 nm in diameter. (Female, 61, polymyositis, left biceps). Bar = 1.0 μm.

FIG. 8. A premyocyte contained some myofibrils (M) and polyribosomes (P). It shared the basement membrane (arrow) with the parent cell. (Female, 60, polymyositis, left pectoralis major). Bar = 1.0 μm.

development of premyocytes were observed (fig. 8). The formation of the thin filaments and Z line material seemed to precede that of thick filaments. On one occasion, annulate lamellæ were seen in the cytoplasm of the satellite cells. An aberrant cilium was encountered in a premyocyte of one case (fig. 9).

2. *Changes in the blood vessels.* Multi-layering of the basement membrane of the blood vessels was noted in 20 (62.5 per cent) of 32 cases of polymyositis and dermatomyositis. The endothelial cells of the vessels were hypertrophied in 18 (56 per cent) of these 32 cases. They contained increased numbers of organelles including mitochondria and polyribosomes, prominent Golgi apparatus and centrioles.

Three kinds of inclusions were noted in the endothelial cells, (1) granulotubular inclusions, (2) electron dense rods (Weibel-Palade bodies) and (3) filamentous material. (1) A thin membrane similar to endoplasmic reticulum surrounded the granulotubular inclusions which consisted of clusters of granules some with

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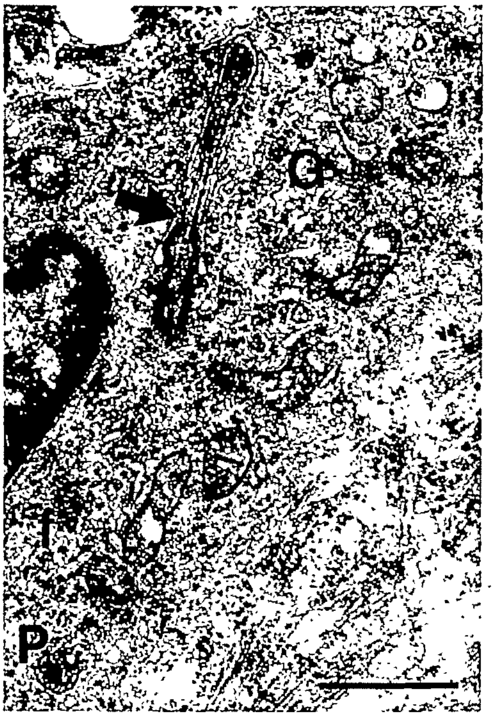

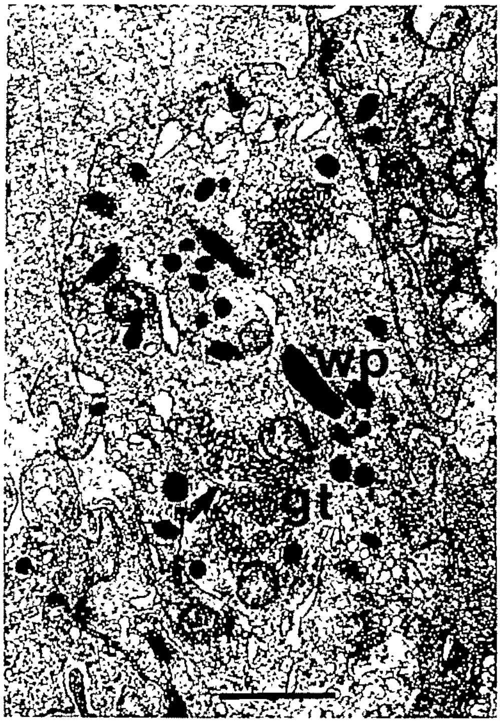

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FIG. 9. The cytoplasm of a premyocyte was rich in polyribosomes (P) and contained fine filaments (f). A Golgi apparatus (G) was present as well as an aberrant cilium (arrow). (Female, 11, polymyositis, left biceps). Bar = 1.0μm.

FIG. 10. In the endothelial cell of a capillary, granulotubular inclusions (gt) were surrounded by membrane (arrow) similar to the endoplasmic reticulum. The endothelial cell also harboured numerous electron-dense rod-shaped inclusions, Weibel-Palade bodies (WP). (Female, 45, polymyositis with breast cancer, left triceps). Bar = 1.0 μm.

elongated contours and a tubular structure (fig. 10). The diameter of these granules or tubules was 25–35 nm. Granulotubular inclusions were found in two cases of polymyositis, one associated with Sjögren's syndrome and another with carcinoma of the breast. (2) The electron dense laminated rods (Weibel-Palade bodies) (fig. 10) were 180–240 nm wide and 180–880 nm long. They had three to six narrow electron-lucent zones which ran parallel to the long axis of the inclusions. They were particularly abundant in four cases of polymyositis including one with carcinoma of the breast. (3) Some endothelial cells presented filamentous material about 10 nm in diameter. In one case of dermatomyositis, an arrangement of thin and thick filaments as in striated myofilbrils was observed in a group of cells which were surrounded by a common basement membrane (fig. 11) and presented tight junctions between the cells: lymphocytes were enclosed by these cells. These features suggest that these cells were the endothelial cells of a blood vessel.

A marked difference was occasionally noted in the electron density of the cytoplasm of the endothelial cells of the same vessel. Some endothelial cells had electron-lucent cytoplasm while others had much more electron-dense cytoplasm. In the two cases of dermatomyositis, numerous large vacuoles were present in some endothelial cells of the vessels.

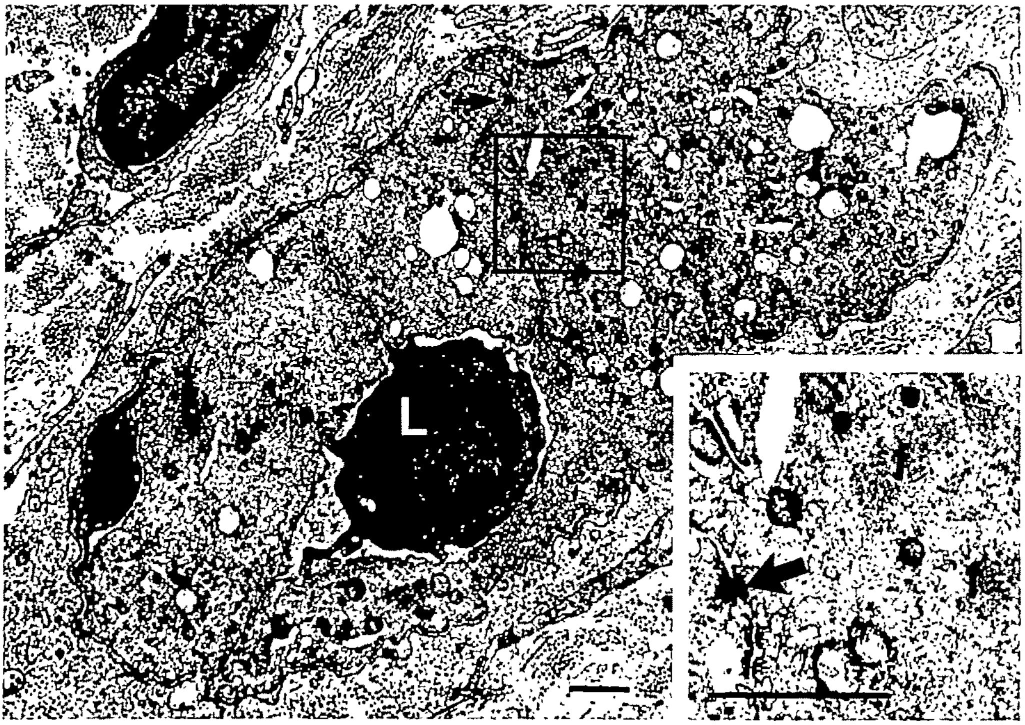

FIG. 11. Four cells were enclosed in a common basement membrane; the adjacent cells had tight junctions (arrows). As seen in the *inset*, some cells contained thin and thick filaments (f) which were similar to those of myofibrils. In the space surrounded by these cells, a lymphocyte (L) was present. This structure may represent an altered blood vessel. (Male, 48, dermatomyositis, left quadriceps femoris). Bar = 1.0 μm.

3. *Inflammation.* Macrophages, lymphocytes, mast cells, plasma cells, monocytes and a small number of eosinophils and basophils were recognized in the interstitial tissue. There was a marked variation in the degree of inflammatory reaction in the connective tissue from case to case. Four patients, who were on steroids at the time of the muscle biopsy, showed much less inflammatory reaction than other cases. Macrophages were seen in all the cases, lymphocytes in 88 per cent of the cases, mast cells in 69 per cent, plasma cells in 50 per cent and monocytes in 19 per cent.

Eosinophils were seen in 2 of 32 cases, both were cases of polymyositis, one associated with rheumatoid arthritis and another without other disorder. Basophils were noted in only one case with polymyositis.

Plasma cells were particularly abundant in three cases of polymyositis, one associated with Sjögren's syndrome, one with carcinoma of the lung and one without other disorder. Amongst 28 cases of polymyositis and dermatomyositis who were not on steroids at the time of the biopsy, plasma cells were present in 16 and absent in 12.

In the 16 cases showing plasma cells, the mean duration of the muscle symptoms was 3.33 ± 0.82 years (mean ± standard error of the mean) and the serum creatine-phosphokinase level was 594 ± 159 IU/l. ($n = 15$). In 12 cases which did not show plasma cells, the corresponding figures were 3.41 ± 1.11 years and 743 ± 219 IU/l. ($n = 11$). Neither the difference in the duration of the muscle symptoms nor the CPK levels was significant ($P > 0.2$).

Amongst the lymphocytes were some with prominent nuclei and an increased amount of cytoplasm which was rich in ribosomes and had increased numbers of the mitochondria and prominent Golgi apparatus and sometimes rough endoplasmic reticulum (fig. 13). These features of some of the lymphocytes were consistent with their being transformed or activated lymphocytes.

Some macrophages, lymphocytes and a small number of plasma cells were seen between the basement and plasma membranes of the muscle fibres (figs. 12 and 14).

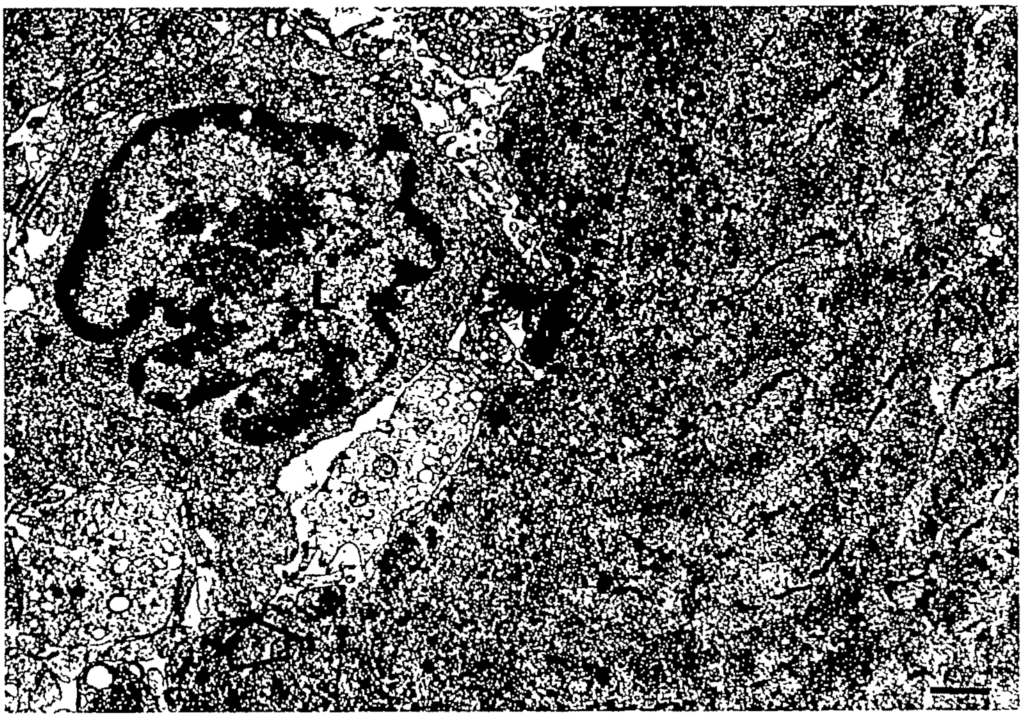

FIG. 12. Cytoplasmic processes of macrophages and lymphocytes (L) were seen inside the basement membrane of the muscle fibres and lay in contact with the plasma membrane of the fibre (open arrows). The myofibrils showed smearing of the Z line material at the place where the leucocytes contacted the muscle plasma membrane. (Male, 54, polymyositis, left biceps). Bar = 1.0 μm.

Macrophages were seen in such a location in 26 of 32 cases, lymphocytes in 13 cases and plasma cells in 3 cases. Many leucocytes were in direct contact with the plasma membrane of the muscle fibres; cell processes of various size were often extended from these leucocytes to the plasma membrane of the muscle (fig. 12). The myofibrils beneath the plasma membrane, which was in close contact with the leucocytes, commonly showed changes such as loss of myofilaments and streaming or smearing of the Z lines. In two cases, some cells inside the basement membrane of the muscle fibre were undergoing mitosis; their origin was uncertain.

In the interstitial tissue, besides the inflammatory cells, fibroblasts and collagen fibres were frequent both around the vessels and between the muscle fibres.

4. *Intramuscular nerves, motor end-plates and muscle spindles.* Specimens which contained enough intramuscular nerves for examination were obtained in six cases. Although most of the nerves were free from pathological change, occasional changes were present in the axons, myelin sheaths and in Schwann cell cytoplasm:

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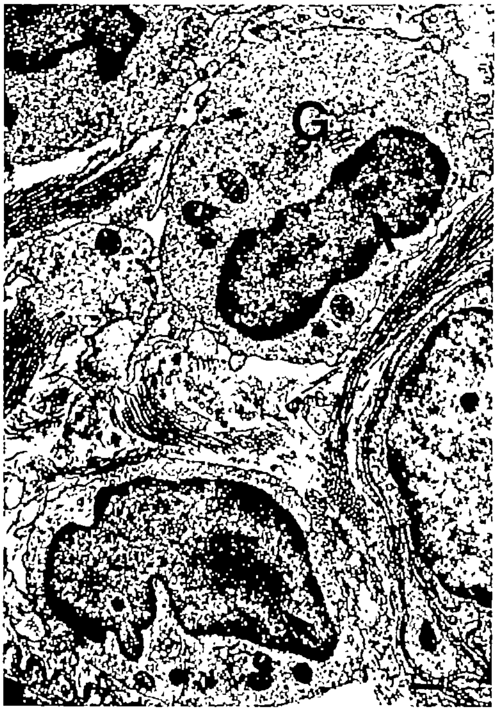

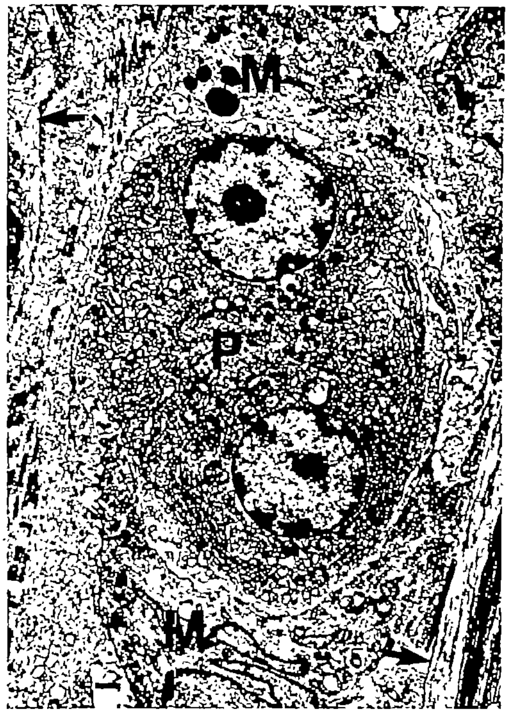

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FIG. 13. The nuclei of some lymphocytes had prominent nucleoli (arrows), more cytoplasm than usual and contained polyribosomes, mitochondria and prominent tubules of the Golgi apparatus (G). These cells had features of transformed lymphocytes. (Female, 69, polymyositis, left deltoid). Bar = 1.0 μm.

FIG. 14. A plasma cell (P) with two nuclei along with macrophages (M) occurred inside the basement membrane (arrows) of a muscle fibre which showed marked decrease in its contractile material. (Female, 66, polymyositis with carcinoma of the bronchus, right biceps). Bar = 1.0 μm.

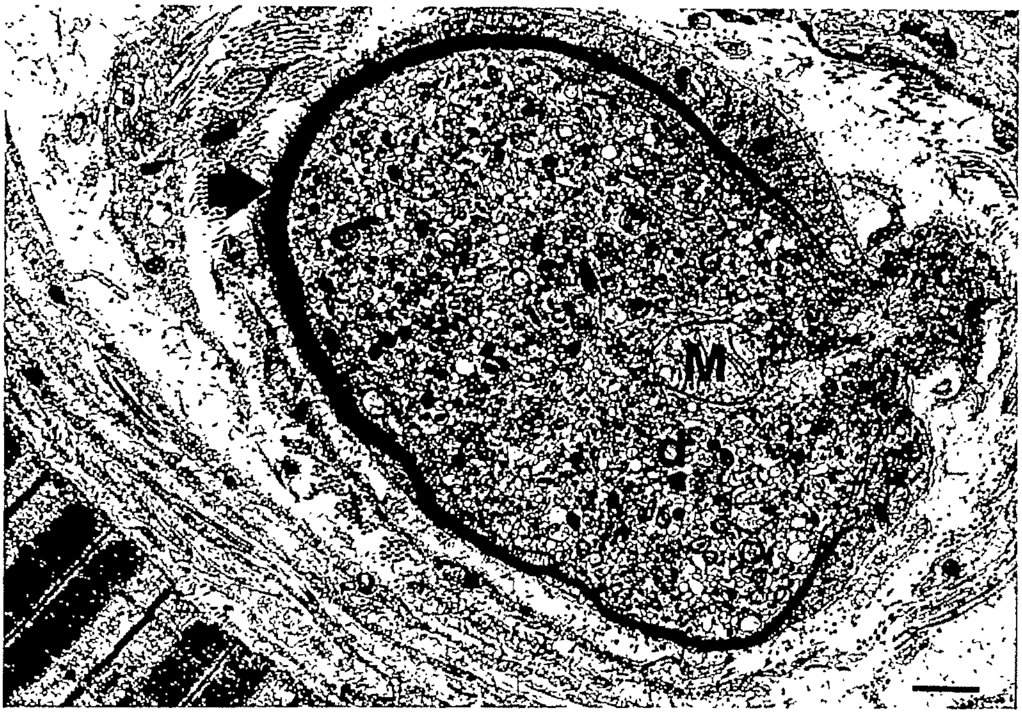

FIG. 15. The axon of an intramuscular nerve of large diameter had a very thin myelin sheath (arrow). The axon which showed evidence of degeneration was filled with large numbers of membranous bodies (open arrow), vacuoles, electron-dense granular bodies (d) and mitochondria (M) some of which were unusually large. (Female, 63, polymyositis, right triceps). Bar = 1.0 μm.

Some large axons (fig. 15) had disproportionately thin myelin sheaths and the axons were packed with electron-dense granular bodies, membranous bodies and vacuoles. Some of the Schwann cell cytoplasm presented myelin figures and electron-dense bodies of various shape and size. Of 6 cases examined, axonal changes were present in 2 cases and changes of the Schwann cells or myelin sheaths were seen in 3 cases.

Motor end-plates were examined by semi-serial sectioning in 5 cases. Twelve end-plates were thus examined and one or more of the following findings were present in 6 of them. The findings included (1) partial or total absence of the terminal nerves from the sole-plates, (2) extension of Schwann cell cytoplasm into the primary synaptic clefts and (3) retraction of the terminal nerves from the sole-plates (fig. 16). The nerve terminals sometimes showed accumulation of glycogen granules, vacuole formation and a decreased number of synaptic vesicles and the formation of electron-dense bodies. The synaptic clefts and the sole-plate showed relatively few changes, they consisted of dilatation of the secondary synaptic clefts or a decrease in their number in consecutive sections.

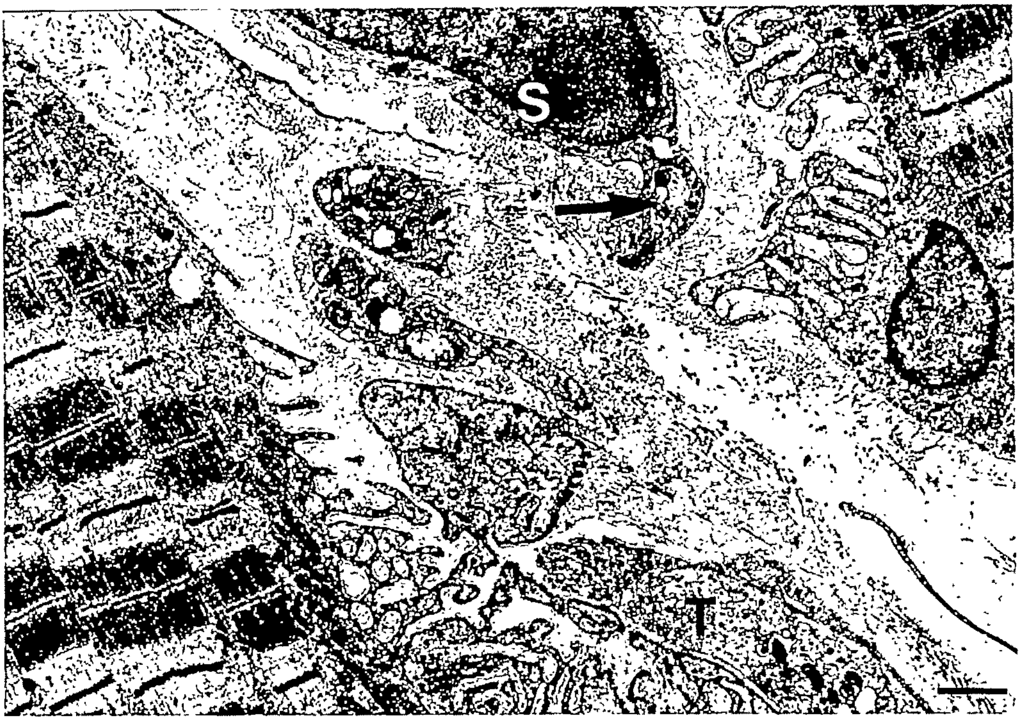

FIG. 16. Two motor end-plates were seen on neighbouring muscle fibres. In neither of them were the synaptic folds in close contact with the nerve terminals over their whole extent. The Schwann cell (S) cytoplasm on the top enclosed a small electron-lucent area (arrow) which may be a nerve terminal retracted from its contact with the muscle fibre. The synaptic folds of the motor end-plate in the bottom were in contact with the nerve terminal (T) over a limited area only. (Female, 63, polymyositis, right triceps). Bar = 1.0 μm.

A muscle spindle was examined in one of the cases. The changes in the intrafusal space were much less severe than in the extrafusal space. Some of the intrafusal muscle fibres presented rods of Z line material. Some nerve fibres contained electron-dense material. Occasional blood vessels were surrounded by leucocytes. Nearby the intrafusal muscle fibres were folds of basement membrane. These folds sometimes surrounded unmyelinated axons or structures which were rich in mitochondria and had an appearance similar to the sensory endings of the intrafusal muscle fibres.

DISCUSSION

Changes such as multi-layering of the basement membrane and indentation of the surface of the muscle fibres seen in the present series were noted by earlier workers on polymyositis (Minz, González-Angulo, Fraga and Zavala, 1968; Ingold and Jerusalem 1972). As was reported by Shafiq, Milhorat and Gorycki

(1967*a*) and others, the plasma membrane disappears in degenerating muscle fibres in polymyositis, but this occurs also in many other diseases such as Duchenne muscular dystrophy (Milhorat, Shafiq and Goldstone, 1966).

Along with the loss of myofibrils, the wide variety of alterations of the contractile material noted in the present series included streaming and rod formation of the Z lines, double Z lines, cytoplasmic bodies, ring fibres and sacroplasmic masses. As noted by Vick (1970), the thin myofilaments and Z lines tended to be damaged more severely than the thick myofilaments. The contrary was seen in one case which showed selective loss of the thick myofilaments similar to the change reported by Carpenter, Karpati, Rothman and Watters (1976) in childhood dermatomyositis. Cytoplasmic bodies have been reported in various conditions including polymyositis (Shafiq *et al.*, 1967*a*; Hughes and Esiri, 1975). In the present series, ring fibres and sarcoplasmic masses co-existed in two cases. Such co-existence has been noted by earlier authors (Bethlem and Wijngaarden, 1963).

The number of mitochondria in the muscle fibres varied considerably as already reported by Hughes and Esiri (1975). Large mitochondria and crystalline mitochondrial inclusions were also found, as had been reported by Shafiq, Milhorat and Gorycki (1967*b*) and Chou (1969). Many authors including Ingold and Jerusalem (1972) have commented on the dilatation of the lateral sacs of the sarcoplasmic reticulum in polymyositis and this was noted in many cases of the present series.

The rough endoplasmic reticulum occurs in fœtal muscle (Ochoa and Mair, 1968), satellite cells (Ishikawa, 1970) and regenerating muscle fibres in polymyositis (Mastaglia and Walton, 1971), but it is of unusual occurrence in mature muscle fibres. In the present series, rough endoplasmic reticulum was seen not only in the satellite cells and premyocytes but also in apparently mature muscle fibres. Moreover in one case rough endoplasmic reticulum was continuous with a concentric arrangement of tubules (fig. 2), suggesting that the rough endoplasmic reticulum may be one of the origins of the concentric structures in the muscle fibres. Furthermore, the Golgi apparatus, usually inconspicuous in normal muscle fibres, was prominent in the muscle fibres of many of the cases in this series. Structures similar to the Golgi apparatus were reported by Mastaglia and Walton (1971) in polymyositis.

The ultrastructure of annulate lamellæ was studied by Kessel (1968), Wischnitzer (1970) and others. The annulate lamellæ most commonly occur in rapidly proliferating or developing cells such as embryonic cells and tumour cells, but have been observed also in cultured cells infected with various viruses (Koestner, Kasza and Kindig, 1966; Merkow, Slifkin, Pardo and Rapoza, 1970; Patrizi and Middelkamp, 1970). There has been, to our knowledge, only one previous reference to this structure in human skeletal muscles by Chou (1968). In his report on myxovirus-like structures in chronic polymyositis he mentioned 'excessive membrane structure resembling annulate lamellæ' within or surrounding intranuclear vacuoles and also in the cytoplasm near filamentous aggregates which he called myxovirus-like structures. In the present series, in two cases which showed annulate lamellæ, some other muscle fibres presented thick filamentous inclusions similar to Chou's virus-like inclusions. This may suggest some relationship between annulate lamellæ and thick filamentous inclusions. Wischnitzer (1970) thought that annulate lamellæ may derive from the outer nuclear envelope and give rise to the endoplasmic reticulum to meet the intensive metabolic needs of the cells. In relation to viral infection, Merkow *et al.* (1970) stated that annulate lamellæ may reflect either a cellular response concomitant with virus replication or may be a secondary manifestation of viral toxicity. The presence of rough endoplasmic reticulum, prominent Golgi apparatus and annulate lamellæ all seem to suggest an active metabolic state, in particular, enhanced protein synthesis by the cells and probably represents repair and regeneration of the muscle fibres.

Zebra bodies and tubular aggregates were seen only infrequently in the present series. Neither of these structures have been reported previously in polymyositis. The same applies to the concentric laminated structures (fig. 4) each lamina of which had a beaded appearance. A similar structure has been reported in infantile spinal muscular atrophy (Roy, Dubowitz and Wolman, 1971), in alcoholic polyneuropathy (Mair and Tomé, 1972) and many other conditions. From these reports, it is clear that these concentric bodies are not specific for any particular disease of muscle.

Thin filamentous inclusions (fig. 5) had been reported in hypokalæmic periodic paralysis (Odor, Patel and Pearce, 1967) and also in normal muscle (Shafiq, Gorycki, Goldstone and Milhorat, 1966). Their origin was uncertain. Although Odor *et al.* (1967) suggested the myofilaments as a possible origin, the thin filamentous inclusions in the present series were thinner than the thin myofilaments and also thinner than the filaments reported by Schochet and McCormick (1973) in polymyositis.

The thick filamentous inclusions (fig. 6) were similar to those described by Chou (1968) and Sato, Walker, Peter, Reese and Chou (1971) as myxovirus-like inclusions and also to the inclusions described by Yunis and Samaha (1971). Similar structures have been reported in two cases of chronic myositis by Jerusalem, Baumgartner and Wyler (1972), and by Fidziańska (1973) and Hughes and Esiri (1975) in polymyositis.

Carpenter, Karpati and Eisen (1975) saw these inclusions in 4 of their 20 cases of polymyositis and thought this group had common clinical features, namely, chronic adult polymyositis unassociated with collagen disease. These clinical features were also exhibited by the 3 cases with thick filamentous inclusions in the present series. Accordingly, it seems reasonable to consider these cases as a subgroup of polymyositis.

Myxovirus-like inclusions reported in muscle by Greco, Askenase and Kashgarian (1977) were spheroid with projections and appeared different from these filamentous inclusions discussed above.

Among the viruses of vertebrates, the filamentous structure is a conspicuous feature of the myxovirus and paramyxovirus groups. The myxovirus and paramyxovirus groups were referred to as myxoviruses group I and II, respectively, by some authors. The nucleocapsids of myxoviruses are believed to be 6–9 nm in diameter, while those of the paramyxovirus group are about 18 nm in diameter (Fenner and White, 1970). However, there is considerable pleomorphism among these nucleocapsids. The nucleocapsids of the paramyxoviruses, which are similar in size to the thick filamentous inclusions in the present series, consist of a large number of protein capsomeres attached to the viral RNA molecule in the form of a helix. The morphological features of nucleocapsids of measles virus, one of the paramyxoviruses, in infected cells were studied by Nakai, Shand and Howatson (1969) and others. They reported wavy filaments with cross striation and sometimes with a helical structure.

In the present series, thick filamentous inclusions had not any distinct striation or helical arrangement. Because of known pleomorphism of these viruses, however, it is difficult to rule out the possibility that these thick filamentous inclusions may be the nucleocapsids of paramyxoviruses. Virological studies in an attempt to isolate viruses were not carried out in the present series. Yunis and Samaha (1971) pointed out the close resemblance of the thick filamentous inclusions to the thick myofilaments. The relationship between the intranuclear and sarcoplasmic filamentous inclusions remains unsolved but Masurovsky, Benitez, Kim and Murray (1970) considered that some intranuclear inclusions may be the source of the cytoplasmic filamentous inclusions.

Prominent regeneration of the muscle fibres is a salient feature of polymyositis. Shafiq, Gorycki and Milhorat (1967) stated that muscle regeneration is more prominent in polymyositis than in muscular dystrophy. In our observations at the later stage of regeneration, while some premyocytes lay adjacent to each other without basement membrane between them, others had a common layer of the basement membrane between them. This was suggestive of the possibility that some regenerating muscle fibres fuse while some others become independent. This was consistent with the view of Chou and Nonaka (1977) who thought that the fate of regenerating muscle cells varies depending on the type and extent of the injury to the muscle and the state of innervation of the sarcolemmal tube. The presence of annulate lamellæ in satellite cells was noted in one case and probably reflects the activated metabolism of the cells. An aberrant cilium was seen in a premyocyte of one case and has been reported by Bergman, Johns and Afifi (1971) in a case of myasthenia gravis.

Hypertrophy of the endothelial cells of the blood vessels was noted in 56 per cent of the cases of the present series. It has been described in myositis by many authors, including Shafiq *et al.* (1967*a*), González-Angulo, Fraga, Minz and Zavala (1968) and Jerusalem, Rakusa, Engel and Macdonald (1974). The cause of the hypertrophy is not clear but according to Nightingale and Hurley (1978) who studied experimental chronic inflammation in rats, massive sustained migration of the lymphocytes through the vessel wall may well cause this change.

In the present series, three kinds of cytoplasmic inclusions, namely, (1) granulotubular inclusions, (2) electron-dense laminated rods, and (3) filamentous material were encountered in the endothelial cells of the blood vessels. The granulotubular inclusions (fig. 10) were similar to those reported by Norton (1970), Hashimoto, Robinson, Velayos and Niizuma (1971), Jerusalem *et al.* (1974) and many others in cases of dermatomyositis, and Lapresle and Gray (1973) in polymyositis. Similar structures have been described in endothelial cells in systemic lupus erythematosus (Norton, 1969), leukæmia (Recher, Sinkovics, Sykes and Whitescarver, 1969), Sjögren's syndrome (Shearn, Tu, Stephens and Lee, 1970) and herpes simplex encephalitis (Baringer, 1971). Although some authors pointed out the similarity of these inclusions to the nucleocapsids of paramyxoviruses (Hashimoto *et al.*, 1971), virological evidence has been lacking; others prefer the view that they represent a cellular reaction to some unknown factors (Schaff, Heine and Dalton, 1972).

The electron-dense laminated rods (fig. 10) in this series were identical to the structures reported by Weibel and Palade (1964) in the endothelial cells of small arteries in rat and man. Later, several authors have reported them in normal conditions and in disorders such as rheumatoid arthritis (Highton, Caughey and Rayns, 1966) and brain tumour (Hassoun, Hirano and Zimmerman, 1975). Norton (1970) saw them in the intramuscular blood vessels in scleroderma. Matsuda and Sugiura (1970) thought that they originate from the Golgi apparatus.

Fine filaments are known to occur in normal endothelial cells (Rhodin, 1967) and it was postulated by Gabbiani, Badonnel and Rona (1975), who saw them in the aorta of hypertensive rats, that some of them may be actin filaments and may contract. Moreover, cross striation of the filaments was reported by Giacomelli, Wiener and Spiro (1970). In one case of dermatomyositis in the present series, thin and thick filaments arranged as in striated myofibrils were observed in a group of cells which resembled endothelial cells of the blood vessels (fig. 11). This suggested the formation of contractile material within the endothelial cells. Filaments were noted in the endothelial cells of the vessels in the muscle in childhood dermatomyositis by Banker (1975).

The presence of numerous vacuoles and lipid bodies and a decreased number of organelles in the endothelial cells were noted in two cases of dermatomyositis in this series. These findings may suggest the possibility that changes in the blood vessels in dermatomyositis differ somewhat from those in polymyositis; the endothelial cells often show vacuoles and sometimes prominent filamentous inclusions in dermatomyositis. Although cases of dermatomyositis in the present series were too few to draw any conclusion, Banker (1975) described similar vacuolar formation in the vessels in cases of childhood dermatomyositis. Carpenter, Karpati and Melmed (1977) examined 13 adult cases of dermatomyositis and saw marked changes in the blood vessels including destruction of the small vessels and attributed some of the changes of the muscle fibres to ischemia.

Electron-lucent swollen endothelial cells adjacent to more electron-dense cells were seen occasionally in this series and a similar change has been reported not only in various inflammatory myopathies (Jerusalem *et al.*, 1974; Banker, 1975), but also in muscular dystrophy (Koehler, 1977). The significance of this finding is uncertain, but may indicate a different metabolic state in adjacent endothelial cells.

Multi-layering of the basement membrane of the blood vessels was seen in about 60 per cent of the present series. Jerusalem *et al.* (1974) saw this change in 47 per cent of cases of polymyositis. However, it is not specific for polymyositis but has been reported in various conditions such as diabetes mellitus (Banson and Lacy, 1964), systemic lupus erythematosus (Norton, 1970) and muscular dystrophy (Koehler, 1977).

The predominance of macrophages and lymphocytes and the paucity of neutrophils in the interstitial tissue noted in this series is in accordance with the findings of Hughes and Esiri (1975). There was no obvious relationship between duration of disease and frequency of these infiltrating cells. Some lymphocytes had the features of transformed or activated lymphocytes as already reported by Mastaglia and Walton (1971), Hughes and Esiri (1975) and De Reuck, De Coster and Inderadjaja (1977). Transformation of lymphocytes is known to occur in a wide variety of circumstances including the presence of various chemical substances, toxins and antigens to which the subject has been sensitized (Bessis, 1972). Close apposition of lymphocytes and macrophages to the plasma membrane of the muscle fibres in the cases of myositis was described by Mastaglia, Dawkins and Papadimitriou (1974) and Hughes and Esiri (1975) and was also noticed in the present series. A similar phenomenon was demonstrated in experimental allergic myositis (Currie, 1971) and transplanted muscles (Mastaglia *et al.*, 1974). This may suggest that in polymyositis the muscle fibres are damaged by the lymphocytes which have been sensitized to the muscle fibres as in experimental allergic myositis. However, this phenomenon is known to occur in various conditions (Shelton and Dalton, 1959) and has not been proven to be specific to the cell-mediated immune reaction.

In the present series, plasma cells were seen in 50 per cent of the cases, but Hughes and Esiri (1975) saw them in only 2 of their 13 cases. A case of Sjögren's syndrome showed abundant plasma cells in the interstitial tissue. This was consistent with the cases reported by Silberberg and Drachman (1962, Case 2) and Fox and Hill (1966). However, a similar degree of plasma cell infiltration was present in other cases of polymyositis, including a case associated with carcinoma.

According to our data, the presence of plasma cells reflected neither long duration of the muscle symptoms nor a high creatine-phosphokinase level which is related probably to the destruction of the muscle fibres. The presence of plasma cells inside the basement membrane of the muscle fibres has not been reported previously in polymyositis. The significance of this finding is not clear. Since plasma cells are known to play an important role in the production of immunoglobulins, their occurrence may raise the question as to whether humoral antibody is involved in some cases of polymyositis at tissue level. Whitaker and W. K. Engel (1972) demonstrated deposits of immunoglobulin in the vessel walls in some cases of myositis particularly in childhood dermatomyositis. In some instances, autoimmune states are produced by the combined action of a cell-mediated immune mechanism and humoral antibodies (Allison, 1977).

Involvement of intramuscular nerves in polymyositis was discussed by various authors in the 1950s when the terms 'distal neuronitis' or 'neuromyopathy' were proposed (Richardson, 1956; Cōers and Woolf, 1959). In the present series the majority of the nerves were intact, but in 5 of the 6 cases where the intramuscular nerves were examined a small proportion of the nerves showed changes.

The interpretation of the morphological changes in the motor end-plates is difficult mainly because of marked normal variation. Focal absence of nerve terminals and simplified synaptic folds are known to occur in a small proportion of the control specimens examined by A. G. Engel, Jerusalem, Tsujihata and Gomez (1975). However, in the present series 6 of 12 motor end-plates examined showed various kinds of changes which caused loss of the intimate contact between the nerve terminal and the sole-plate and the relatively high frequency of this finding strongly suggests that some of the changes reflect a pathological process.

In the present study, some ultrastructural changes of the muscle spindle were described in one case. In the past, light microscopical changes of the muscle spindles in myositis were reported by Greenfield, Shy, Alvord and Berg (1957), Lapresle and Milhaud (1964), Cazzato and Walton (1968) and Banker and Victor (1966). The present study supports the view that the changes in the muscle spindle are much less severe than in the extrafusal space, although cellular infiltration and changes of the intrafusal muscle fibres were present.

SUMMARY

Muscle biopsies from 32 cases with polymyositis and dermatomyositis were examined by electron microscopy. Most of the changes of the muscle fibres were non-specific and little structural difference was seen in the various clinical types. The muscle fibres sometimes showed rough endoplasmic reticulum, annulate lamellæ and prominent Golgi apparatus. Thin and thick filamentous inclusions were present both in the sarcoplasm and nuclei of some muscle fibres. Thick filamentous inclusions were seen in chronic cases and were sometimes associated with annulate lamellæ. Regeneration of muscle was often conspicuous. The endothelial cells of the blood vessels were hypertrophied; some cells contained granulotubular inclusions, rod-shaped bodies (Weibel-Palade bodies) and filamentous material. The basement membrane of the vessels was often multi-layered. The cells infiltrating the interstitial tissue included macrophages, lymphocytes, transformed lymphocytes, plasma cells, monocytes, mast cells and only occasional eosinophils and basophils. Lymphocytes, macrophages and a few plasma cells were seen between the plasma and basement membranes of degenerating muscle fibres. Changes were also noted in some intramuscular nerves, motor end-plates and a muscle spindle.

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REFERENCES

Allison, A. C. (1977) Autoimmune diseases: Concepts of pathogenesis and control. In: *Autoimmunity. Genetic, Immunologic, Virologic and Clinical Aspects.* Edited by N. Talal. New York: Academic Press, pp. 91–139.

Banker, B. Q. (1975) Dermatomyositis of childhood. Ultrastructural alterations of muscle and intramuscular blood vessels. *Journal of Neuropathology and Experimental Neurology*, **34**, 46–75.

—— and Victor, M. (1966) Dermatomyositis (systemic angiopathy) of childhood. *Medicine, Baltimore*, **45**, 261–289.

Banson, B. B. and Lacy, P. E. (1964) Diabetic microangiopathy in human toes with emphasis on the ultrastructural change in dermal capillaries. *American Journal of Pathology*, **45**, 41–58.

Baringer, J. R. (1971) Tubular aggregates in endoplasmic reticulum in herpes-simplex encephalitis. *New England Journal of Medicine*, **285**, 943–945.

Bergman, R. A., Johns, R. J. and Afifi, A. K. (1971) Ultrastructural alterations in muscle from patients with myasthenia gravis and Eaton-Lambert syndrome. *Annals of the New York Academy of Sciences*, **183**, 88–122.

Bessis, M. (1972) *Cellules du Sang Normal et Pathologique.* Paris: Masson et Cie.

Bethlem, J. and Wijngaarden, G. K. (1963) The incidence of ringed fibres and sarcoplasmic masses in normal and diseased muscle. *Journal of Neurology, Neurosurgery and Psychiatry*, **26**, 326–332.

Carpenter, S., Karpati, G. and Eisen, A. (1975) A morphologic study of muscle in polymyositis: Clue to pathogenesis of different types. In: *Recent Advances in Myology.* Edited by W. G. Bradley, D. Gardner-Medwin and J. N. Walton. Amsterdam: Excerpta Medica, pp. 374–379.

—— —— and Melmed, C. (1977) The adult form of dermatomyositis: A muscle biopsy study. *Neurology, Minneapolis*, **27**, 377–378.

—— —— Rothman, S. and Watters, G. (1976) The childhood type of dermatomyositis. *Neurology, Minneapolis*, **26**, 952–962.

Cazzato, G. and Walton, J. N. (1968) The pathology of the muscle spindle. A study of biopsy material in vascular and neuromuscular diseases. *Journal of the Neurological Sciences*, **7**, 15–70.

Chou, S. M. (1968) Myxovirus-like structures and accompanying nuclear changes in chronic polymyositis. *Archives of Pathology, Chicago*, **86**, 649-658.

—— (1969) 'Megaconial' mitochondria observed in a case of chronic polymyositis. *Acta Neuropathologica, Berlin*, **12**, 68-89.

—— and Nonaka, I. (1977) Satellite cells and muscle regeneration in diseased human skeletal muscles. *Journal of the Neurological Sciences*, **34**, 131-145.

Coërs, C. and Woolf, A. L. (1959) *The Innervation of Muscle. A Biopsy Study*. Oxford: Blackwell, pp. 118-124, 133-134.

Currie, S. (1971) Experimental myositis: The *in-vivo* and *in-vitro* activity of lymph-node cells. *Journal of Pathology*, **105**, 169-185.

De Reuck, J., De Coster, W. and Inderadjaja, N. (1977) Acute viral polymyositis with predominant diaphragm involvement. *Journal of the Neurological Sciences*, **33**, 453-460.

Engel, A. G., Jerusalem, M., Tsujihata, M. and Gomez, M. R. (1975) The neuromuscular junction in myopathies. A quantitative ultrastructural study. In: *Recent Advances in Myology*. Edited by W. G. Bradley, D. Gardner-Medwin and J. N. Walton. Amsterdam: Excerpta Medica, pp. 132-143.

Fenner, F. J. and White, D. O. (1970) *Medical Virology*. New York: Academic Press, pp. 302-312, 313-332.

Fidziańska, A. (1973) Virus-like structures in muscle in chronic polymyositis. *Acta Neuropathologica, Berlin*, **23**, 23-31.

Fox, J. T. Jr. and Hill, C. (1966) Sjögren's syndrome and late-life myopathy. *Archives of Neurology, Chicago*, **15**, 397-398.

Gabbiani, G., Badonnel, M-C. and Rona, G. (1975) Cytoplasmic contractile apparatus in aortic endothelial cells of hypertensive rats. *Laboratory Investigation*, **32**, 227-234.

Giacomelli, F., Wiener, J. and Spiro, D. (1970) Cross-striated arrays of filaments in endothelium. *Journal of Cell Biology*, **45**, 188-192.

González-Angulo, A., Fraga, A., Minz, G. and Zavala, B. (1968) Submicroscopic alteration in capillaries of skeletal muscles in polymyositis. *American Journal of Medicine*, **45**, 873-879.

Greco, T. P., Askenase, P. W. and Kashgarian, M. (1977) Postviral myositis: Myxovirus-like structures in affected muscle. *Annals of Internal Medicine*, **86**, 193-194.

Greenfield, J. G., Shy, G. M., Alvord, E. C. Jr. and Berg, L. (1957) *An Atlas of Muscle Pathology in Neuromuscular Diseases*. Edinburgh and London: Livingstone.

Hashimoto, K., Robinson, L., Velayos, E. and Niizuma, K. (1971) Dermatomyositis. Electron microscopic, immunologic, and tissue culture studies of paramyxovirus-like inclusions. *Archives of Dermatology, Chicago*, **103**, 120-135.

Hassoun, J., Hirano, A. and Zimmerman, H. M. (1975) Fine structure of intercellular junctions and blood vessels in medulloblastoma. *Acta Neuropathologica, Berlin*, **33**, 67-78.

Highton, T. C., Caughey, D. E. and Rayns, D. G. (1966) A new inclusion body in rheumatoid synovia. *Annals of the Rheumatic Diseases*, **25**, 149-155.

Hughes, J. T. and Esiri, M. M. (1975) Ultrastructural studies in human polymyositis. *Journal of the Neurological Sciences*, **25**, 347-360.

INGOLD, W. and JERUSALEM, F. (1972) Polymyositis—elektonenmikroskopische Biopsiebefunde von 12 Fällen. *Fortschritte der Neurologie Psychiatrie und ihrer Grenzgebiete*, **40**, 500–513.

ISHIKAWA, H. (1970) Satellite cells in developing muscle and tissue culture. In: *Regeneration of Striated Muscle and Myogenesis*. Edited by A. Mauro, S. A. Shafiq and A. T. Milhorat. Amsterdam: Excerpta Medica, pp. 167–179.

JERUSALEM, F., BAUMGARTNER, G. and WYLER, R. (1972) Virus-ähnliche Einschlüsse bei chronischen neuromuskulären Prozessen. Elektronenmikroskopische Biopseibefunde von 2 Fällen. *Archiv für Psychiatrie und Nervenkrankheiten*, **215**, 148–166.

—— RAKUSA, M., ENGEL, A. G. and MACDONALD, R. D. (1974) Morphometric analysis of skeletal muscle capillary ultrastructure in inflammatory myopathies. *Journal of the Neurological Sciences*, **23**, 391–402.

KESSEL, R. G. (1968) Annulate lamellae. *Journal of Ultrastructure Research*, Supplement 10, 1–82.

KOEHLER, J. (1977) Blood vessels structure in Duchenne muscular dystrophy. 1. Light and electron microscopic observation in resting muscle. *Neurology, Minneapolis*, **27**, 861–868.

KOESTNER, A., KASZA, L. and KINDIG, O. (1966) Electron microscopy of tissue cultures infected with porcine polioencephalomyelitis virus. *American Journal of Pathology*, **48**, 129–147.

LAPRESLE, J. and GRAY, F. (1973) Étude ultrastructurale du muscle squelettique au cours des polymyosites. *Annales Anatomie pathologique, Paris*, **18**, 195–209.

—— and MILHAUD, M. (1964) Pathologie du fuseau neuro-musculaire. *Revue neurologique*, **110**, 97–122.

MAIR, W. G. P. and TOMÉ, F. M. S. (1972) *Atlas of the Ultrastructure of Diseased Human Muscle*. Edinburgh and London: Churchill Livingstone.

MASTAGLIA, F. L., DAWKINS, R. L. and PAPADIMITRIOU, J. M. (1974) Lymphocyte-muscle cells interactions *in vivo* and *in vitro*. *Journal of the Neurological Sciences*, **22**, 261–268.

—— and WALTON, J. N. (1971) An ultrastructural study of skeletal muscle in polymyositis. *Journal of the Neurological Sciences*, **12**, 473–504.

MASUROVSKY, E. B., BENITEZ, H. H., KIM, S. U. and MURRAY, M. R. (1970) Origin, development, and nature of intranuclear rodlets and associated bodies in chicken sympathetic neurons. *Journal of Cell Biology*, **44**, 172–191.

MATSUBARA, S. (1978) Ultrastructural changes in polymyositis and related disorders. Ph.D. Thesis, London University.

MATSUDA, H. and SUGIURA, S. (1970) Ultrastructure of 'tubular body' in the endothelial cells of the ocular blood vessels. *Investigative Ophthalmology*, **9**, 919–925.

MERKOW, L. P., SLIFKIN, M., PARDO, M. and RAPOZA, N. P. (1970) Pathogenesis of oncogenic simian adenoviruses. 7. The origin of annulate lamellae in LLC-MK2 cells infected with SV30. *Journal of Ultrastructure Research*, **30**, 344–353.

MILHORAT, A. T., SHAFIQ, S. A. and GOLDSTONE, L. (1966) Changes in muscle structure in dystrophic patients, carriers and normal siblings seen by electron microscopy; correlation with levels of serum creatinephosphokinase (CPK). *Annals of the New York Academy of Sciences*, **138**, 246–292.

MINZ, G., GONZÁLEZ-ANGULO, A., FRAGA, A. and ZAVALA, B. (1968) Ultrastructure of muscle in polymyositis. *American Journal of Medicine*, **44**, 216–224.

NAKAI, T., SHAND, F. L. and HOWATSON, A. F. (1969) Development of measles virus *in vitro*. *Virology*, **38**, 50–67.

NIGHTINGALE, G. and HURLEY, J. V. (1978) Relationship between lymphocyte emigration and vascular endothelium in chronic inflammation. *Pathology*, **10**, 27–44.

NORTON, W. L. (1969) Endothelial inclusions in active lesions of systematic lupus erythematosus. *Journal of Laboratory and Clinical Medicine*, **74**, 369–379.

—— (1970) Comparison of the microangiopathy of systemic lupus erythematosus, dermatomyositis, scleroderma, and diabetes mellitus. *Laboratory Investigation*, **22**, 301–308.

—— HURO, E. R., LEWIS, D. C. and ZIFF, M. (1968) Evidence of microvascular injury in scleroderma and systemic lupus erythematosus: Quantitative study of the microvascular bed. *Journal of Laboratory and Clinical Medicine*, **71**, 919–933.

—— VELAYOS, E. and ROBINSON, L. (1970) Endothelial inclusions in dermatomyositis. *Annals of the Rheumatic Diseases*, **29**, 67–72.

OCHOA, J. and MAIR, W. G. P. (1968) The ultrastructure of normal fœtal muscle and fœtal muscle from known dystrophic carriers. In: *Proceedings, 4th Symposium on Research in Muscular Dystrophy*. London: Pitman, pp. 223–239.

ODOR, D. L., PATEL, A. N. and PEARCE, L. A. (1967) Familial hypokalemic periodic paralysis with permanent myopathy. A clinical and ultrastructural study. *Journal of Neuropathology and Experimental Neurology*, **26**, 98–114.

PATRIZI, G. and MIDDELKAMP, J. N. (1970) Development and changes of annulate lamellae complexes in rubella virus-infected RK-13 cells. *Journal of Ultrastructure Research*, **31**, 407–423.

RECHER, L., SINKOVICS, J. G., SYKES, J. A. and WHITESCARVER, J. (1969) Electron microscopic studies of suspension cultures derived from human leukemic and nonleukemic sources. *Cancer Research*, **29**, 271–285.

RHODIN, J. A. G. (1967) The ultrastructure of mammalian arterioles and precapillary sphincters. *Journal oj Ultrastructure Research*, **18**, 181–223.

RICHARDSON, A. T. (1956) Clinical and electromyographic aspects of polymyositis. *Proceedings of the Royal Society of Medicine*, **49**, 111–114.

ROY, S., DUBOWITZ, V. and WOLMAN; L. (1971) Ultrastructure of muscle in infantile spinal muscular atrophy. *Journal of the Neurological Sciences*, **12**, 219–232.

SATO, T., WALKER, D. L., PETER, H. A., REESE, H. H. and CHOU, S. M. (1971) Chronic polymyositis and myxovirus-like inclusions, electron microscopic and viral studies. *Archives of Neurology, Chicago*, **24**, 409–418.

SCHAFF, Z., HEINE, U. and DALTON, A. J. (1972) Ultramorphological and ultracytochemical studies on tubuloreticular structures in lymphoid cells. *Cancer Research*, **32**, 2696–2706.

SCHOCHET, S. S. and MCCORMICK, W. F. (1973) Polymyositis with intranuclear inclusions. A light and electron microscopic study. *Archives of Neurology, Chicago*, **28**, 280–283.

SHAFIQ, S. A., GORYCKI, M., GOLDSTONE, L. and MILHORAT, A. T. (1966) Fine structure of fiber types in normal human muscle. *Anatomical Record*, **156**, 283–302.

—— GORYCKI, M. A. and MILHORAT, A. T. (1967) An electron microscopic study of regeneration and satellite cells in human muscle. *Neurology, Minneapolis*, **17**, 567–574.

SHAFIQ, S. A., MILHORAT, A. T. and GORYCKI, M. A. (1967*a*) An electron-microscope study of muscle degeneration and vascular changes in polymyositis. *Journal of Pathology and Bacteriology*, **94**, 139–147.

—— —— —— (1967*b*) Giant mitochondria in human muscle with inclusions. *Archives of Neurology, Chicago*, **17**, 666–671.

SHEARN, M. A., TU, W. H., STEPHENS, B. G. and LEE, J. C. (1970) Virus-like structures in Sjögren's syndrome. *Lancet*, **i**, 568–569.

SHELTON, E. and DALTON, A. J. (1959) Electron microscopy of emperipolesis. *Journal of Biophysical and Biochemical Cytology*, **6**, 513–514.

SILBERBERG, D. and DRACHMAN, D. A. (1962) Late-life myopathy occurring with Sjögren's syndrome. *Archives of Neurology, Chicago*, **6**, 428–438.

VICK, N. A. (1970) The fine structure of polymyositis, with consideration of capillaries and subcellular organelles. *Neurology, Minneapolis*, **20**, 1062–1068.

WEIBEL, E. R. and PALADE, G. E. (1964) New cytoplasmic components in arterial endothelia. *Journal of Cell Biology*, **23**, 101–112.

WHITAKER, J. N. and ENGEL, W. K. (1972) Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. *New England Journal of Medicine*, **286**, 333–338.

WISCHNITZER, S. (1970) The annulate lamellae. *International Review of Cytology*, **27**, 65–100.

YUNIS, E. J. and SAMAHA, F. J. (1971) Inclusion body myositis. *Laboratory Investigation*, **25**, 240–248.

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INFANTILE NEUROAXONAL DYSTROPHY

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INTRODUCTION

THE presence of spheroid bodies in axons, especially in their distal portions and in presynaptic terminals, has been reported in a variety of physiological (Lampert, 1967; Jellinger and Jirasek, 1971; Seitelberger, 1971) and pathological (Lampert and Pentschew, 1964; Sung, 1964; Schneck, 1966; Sung and Stadlan, 1966; Mei Liu, 1978) conditions, as well as in a number of genetic degenerative disorders of the central nervous system (Jellinger and Jirasek, 1971; Seitelberger, 1971; Torack and Hughes, 1972). Several workers (Jellinger and Jirasek, 1971; Seitelberger, 1971) have regarded those diseases, in which spheroids are a prominent pathological feature, as constituting a spectrum of related conditions, the neuroaxonal dystrophies, ranging from infantile neuroaxonal dystrophy, originally described by Seitelberger (1952, 1953), to Hallervorden-Spatz disease, through various intermediary and atypical forms. The distinction between these types has been mainly founded on neuropathological criteria. In typical cases of this disease spheroid bodies are widely distributed throughout the central nervous system and are numerous in the cerebral cortex, as well as in the spinal cord, brain-stem and basal ganglia (Cowen and Olmstead, 1963; Martin, Trelles and Martin, 1972; Defendini, Markesbery, Mastry and Duffy, 1973). In Hallervorden-Spatz disease, spheroids are less widespread and are found mainly in the basal ganglia, substantia nigra, brain-stem and spinal cord, and cortical involvement is lacking or less marked (Wigboldus and Bruyn, 1968; Brucher, Dom and Robin, 1968; Radermecker and Martin, 1972; Indravasu and Dexter, 1968). In addition to the widespread distribution of the spheroids, cases of infantile neuroaxonal dystrophy display other pathological characters well described by Cowen and Olmstead (1963): (1) systematized atrophies affecting the cerebellar cortex, optic pathways, pyramidal tracts, posterior funiculi, brain-stem nuclei and inferior olivary bodies; (2) massive lipid deposits and a dysmyelinic state in the basal ganglia; (3) diffuse fibrillary gliosis of hemispheric white matter (Martin *et al.*, 1972). The presence of an iron-containing pigment in the basal ganglia was initially considered characteristic of Hallervorden-Spatz disease (Seitelberger, 1952, 1953) but was later recognized in true cases of infantile neuroaxonal dystrophy and is no longer regarded as specific (Defendini *et al.*, 1973).

More recently, the occurrence of spheroid bodies, identical to those in the central nervous system, has been recognized in peripheral nerves (Duncan, Strub, McGarry and Duncan, 1970; Bérard-Badier, Gambarelli, Pinsard, Hassoun and Toga, 1971; Martin and Martin, 1972; Sengel and Stoebner, 1972; Shimono, Ohta, Asada and Kuroiwa, 1976) and especially in nerve endings in intramuscular nerves (Toga, Bérard-Badier, Gambarelli, Pinsard and Hassoun, 1971) and in skin and conjunctiva (Arsenio-Nunes and Goutières, 1978).

As more cases were reported, it became evident that in many patients with the typical neuropathological features of infantile neuroaxonal dystrophy, there was also a monotonous, stereotyped, clinical picture. This comprised slowing, then loss, of motor and mental milestones, starting at the end of the first or during the second year of life, marked hypotonia, early visual disturbances, symmetrical pyramidal tract signs and often evidence of peripheral motor involvement of anterior horn cell type. Seizures and extrapyramidal signs were usually lacking. The course was progressive, with decerebration, dementia and death before the age of 10 years (Cowen and Olmstead, 1963; Huttenlocher and Gilles, 1967; Duncan *et al.*, 1970; Martin *et al.*, 1972).

The situation, however, is confused by the fact that not all cases reported as infantile neuroaxonal dystrophy display the same clinical or pathological features, and that there is no invariable relationship between the pathological and the clinical findings.

The purpose of this paper, which reports eight new cases of infantile neuroaxonal dystrophy diagnosed with the help of biopsy of the central or peripheral nervous system, and reviews critically the relevant literature, is to propose that the clinical picture is at least as important a criterion as the neuropathology in the definition of this disease.

CASE REPORTS

Case 1. O.A., the third child of unrelated Algerian parients, was born after normal gestation and delivery. His two older sibs were healthy. His motor and mental development was normal up to 12 months of age, when he crawled on all fours and uttered a few repeated syllables. From the age of one year he progressively lost acquired skills, stopped moving about and showed decreasing interest in his surroundings. At the age of 25 months, neurological examination showed profound truncal and appendicular hypotonia, poor motility, increased deep tendon reflexes and a bilateral Babinski sign. At 2 years 5 months, pendular nystagmus was evident and the optic discs were pale. Bulbar involvement led to difficulty in swallowing. He lay in a frog-like attitude, with the upper limbs abducted at the shoulders and flexed at the elbows. Wasting was now evident, especially in the lower limbs. The ankle jerks were extremely brisk with associated planar flexion of the toes but the patellar reflexes were difficult to elicit. Grasp and mouthing reflexes were prominent. He responded to external stimuli by complex patterns of flexion-extension of all four limbs. He seemed relatively insensitive to pain, as strong pin-prick was necessary to produce any response. He did not follow objects, blinked in response to a strong light, and the photomotor response was slow. Head circumference was 49 cm (normal).

The CSF was normal, as were glutamic pyruvic transaminase levels in blood and CSF, plasma amino acid chromatography and blood and bone-marrow films. Lactic dehydrogenase was 367 mU/ml (N = 60–160).

The EEG showed a background activity at 7 Hz. In sleep, fast rhythms of 12 Hz of moderate amplitude became apparent. Electromyography revealed definite signs of denervation in the left quadriceps muscle. Motor conduction velocity was normal (55 m s^{-1}) in the left median nerve. The sensory conduction velocity was 43.5 m s^{-1}. The electroretinogram and visual evoked responses were normal. Pneumoencephalography showed a widened fourth ventricle with evidence of cerebellar atrophy and slight dilatation of the left lateral ventricle. A brain biopsy was performed at the age of 2 years 6 months. Numerous spheroids with typical membranotubular structures were shown by electron microscopy, although examination with the light microscope was reported as normal (fig. 1A).

Case 2. This French girl was the first child of non-consanguineous healthy parents. Early development was normal, she sat at 8 months and walked at 14 months. From about the age of 16 months she stopped making progress. A few months later psychomotor retardation was apparent. She was no longer able to stand, and a convergent strabismus developed. She was first admitted to another hospital at 21 months. The fundi were then normal. Electromyography, undertaken because spinal muscular atrophy was suspected, was normal, as was motor conduction velocity of the median nerve (57 m s^{-1}).

At the age of 33 months, she was extremely hypotonic and had no head control. In the lower limbs, however, some spasticity was found in the sural muscles bilaterally and there was mild pes equinovarus, with profound proximal hypotonia and a frog-like posture. Deep tendon reflexes were exaggerated throughout. Tapping the Achilles tendon produced flexion of the toes followed by a brisk extension. Rossolimo and Babinski responses were easily elicited. Vision was grossly preserved but there was bilateral convergent strabismus and pendular nystagmus. The optic discs were now pale and the arteries narrowed. She responded to strong painful stimuli. Head circumference was 48 cm (normal). At 38 months there was, in addition, pooling of secretions in the pharynx and the Achilles tendon jerks were no longer obtainable. Optic atrophy was evident. The CSF was normal, as was chromatography of plasma amino acids. The EEG during wakefulness and sleep at the age of 33 months was entirely made up of a high amplitude fast activity of 16 to 18 Hz unresponsive to eye-opening. A few slow waves were interspersed and occasional spikes, without precise localization, were noted. The electroretinogram was normal. Visual evoked responses were present bilaterally although of reduced amplitude. Skin and conjunctival biopsies were performed at the age of 33 months. Spheroids were demonstrated in the nerve endings of both tissues (*see* Arsenio-Nunes and Goutières, 1978).

Case 3. A French boy, the second child of non-related parents. His brother was normal. Early development was normal and at 11 months of age, he was able to stand alone and appeared mentally bright. From then onwards, he acquired no new skills and at 19 months some regression was evident. He was then admitted to another hospital where marked hypotonia and optic atrophy were found. Visual evoked responses were normal (at that time), as was the CSF.

At the age of 21 months, he was still able to stand alone in spite of his hypotonia. Strabismus and pendular nystagmus were now apparent. The tendon reflexes were exaggerated. Two months later he was no longer able to stand and was markedly kyphotic when sitting. Pyramidal tract signs were marked bilaterally. Optic atrophy was evident, more marked in the left disc. The CSF was repeatedly normal, including electrophoresis in agarose. Examination for lysosomal enzymes in leucocytes gave normal results. The EEG was unremarkable in the waking state. Low amplitude fast rhythms appeared during sleep but normal sleep figures, for example, spindles, were seen. Motor conduction velocity was 41.5 ms^{-1} in the right popliteal nerve. Electromyography of both tibialis anticus, right deltoid and rectus abdominis disclosed a typical neurogenic pattern suggestive of progressive anterior horn cell involvement.

Skin and conjunctival biopsies were performed at the age of 23 months. Spheroids were demonstrated in the nerve endings of both tissues (fig. 1B).

Case 4. B.K. was the first child of consanguineous Tunisian parents, both pairs of grandparents being first cousins. He was born after a thirty-seven-week gestation, weighing 2750 g. Apgar score was 9 at one minute and 10 at five minutes. Initial development was normal. He sat by the age of 7 months, crawled on all fours at 9 months. By 11 months, he was standing and could walk when supported. He was uttering repeated syllables. At the age of 14 months he fell from his bed. A few weeks later, he was noted to be fidgety and stopped progressing. At the age of 16 months, he was no longer able to stand with assistance and pronounced no words. When examined at the age of 26 months, he was unable to sit and had little interest in his surroundings, although he could follow visually. Head circumference was 47.5 cm (−1 SD), height was normal (87 cm) and weight was 9.2 kg (3 SD below the mean). Truncal and appendicular hypotonia was extremely marked and some muscular wasting was evident. The deep tendon reflexes were exaggerated and tapping the ankle jerk elicited repeated flexion of the toes. The optic discs appeared slightly pale with normal vessels. A few nystagmoid jerks were noted. The CSF was normal, including gelose electrophoresis. Determination of lysosomal enzymes in leucocytes gave normal results. A CT scan showed no abnormality. The EEG, which had been unremarkable at the age of 19 months, displayed, at 26 months, widespread fast rhythms, unresponsive to stimulation, especially during sleep. Some normal background activity was still present when he was awake. Electromyographic examination of the right tibialis anticus, right common extensor of the toes, right sural and quadriceps muscles was unremarkable. Motor conduction velocity was 40 $m\ s^{-1}$ in the right lateral popliteal nerve. The electroretinogram was normal. Visual evoked responses were of very small amplitude and the physiological components were almost unrecognizable. The somæsthetic evoked responses obtained by stimulation of the median nerve at the wrist were of higher amplitude on the right than on the left side. The latency was markedly increased on both sides (12 ms).

Conjunctival and skin biopsies performed at 26 months of age contained typical spheroid bodies in the small nerves (fig. 1C).

Case 5. L.C., a French girl, the first child of non-consanguineous parents, developed normally until the age of 11 months, when she was beginning to walk. She then lost interest in her surroundings and by 16 months was no longer able to walk or to stand. Deterioration progressed stepwise and, at the age of 21 months, she was markedly hypotonic and could not sit unsupported. By 23 months she was lying in the frog position and her motility was very limited. Facial expression was lacking and proximal limb amyotrophy was evident. The deep tendon reflexes were exaggerated throughout and bilateral Rossolimo and Babinski responses were elicited. Convergent strabismus was noted and the optic discs were atrophic. She reacted to nociceptive stimuli by stereotyped triple flexion. The EEG consisted almost exclusively of diffuse, high amplitude fast rhythms of 20 to 22 Hz predominating in the central areas and unresponsive to eye opening (fig. 2). Motor nerve conduction velocity was 56 $m\ s^{-1}$ in the left popliteal nerve. The electromyogram was interpreted as showing a pattern of mild denervation. The CSF was normal. No abnormal cells were detected in the blood or bone marrow. Arylsulphatase A was present in normal amount. A cortical biopsy at the age of 31 months showed numerous spheroid bodies located in the neuropil in close connection with neuronal somata. The

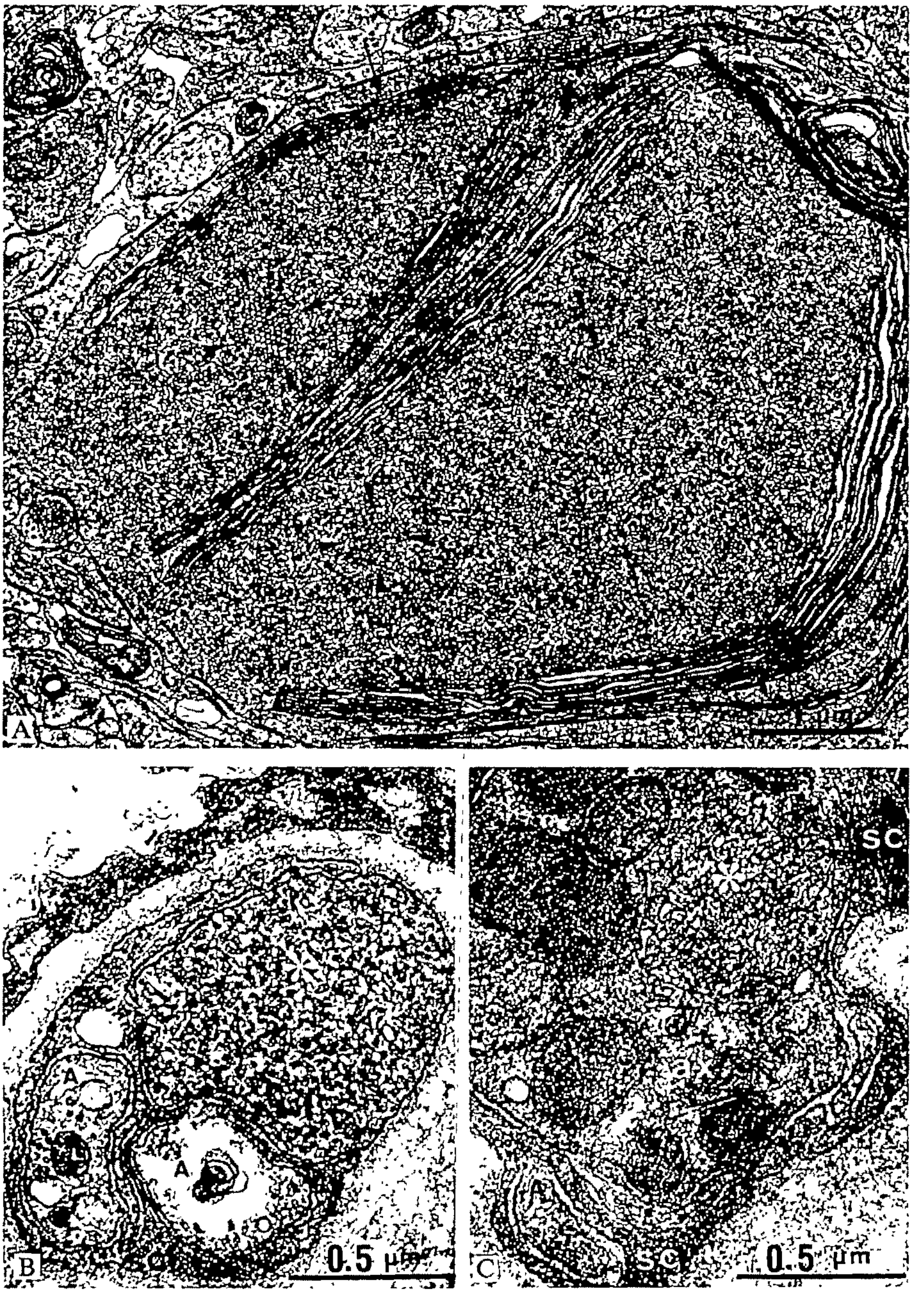

FIG. 1. A, *Case 1*. Cortical biopsy. Large spheroid within an enlarged axon. The membranous and tubular structures form some crystalloid bodies (arrowheads). Bundles of parallel membranes lie peripherally and across the spheroid body (arrows). B, *Case 3*. Skin biopsy. An unmyelinated axon completely filled with a spheroid (asterisk) and two other axons (A) devoid of spheroids are encircled by the same Schwann cell (sc). C, *Case 4*. Conjunctival biopsy. Unmyelinated axon (ax) containing a spheroid (asterisk) and numerous mitochondria. A normal axon (A) is surrounded by the same Schwann cell (sc).

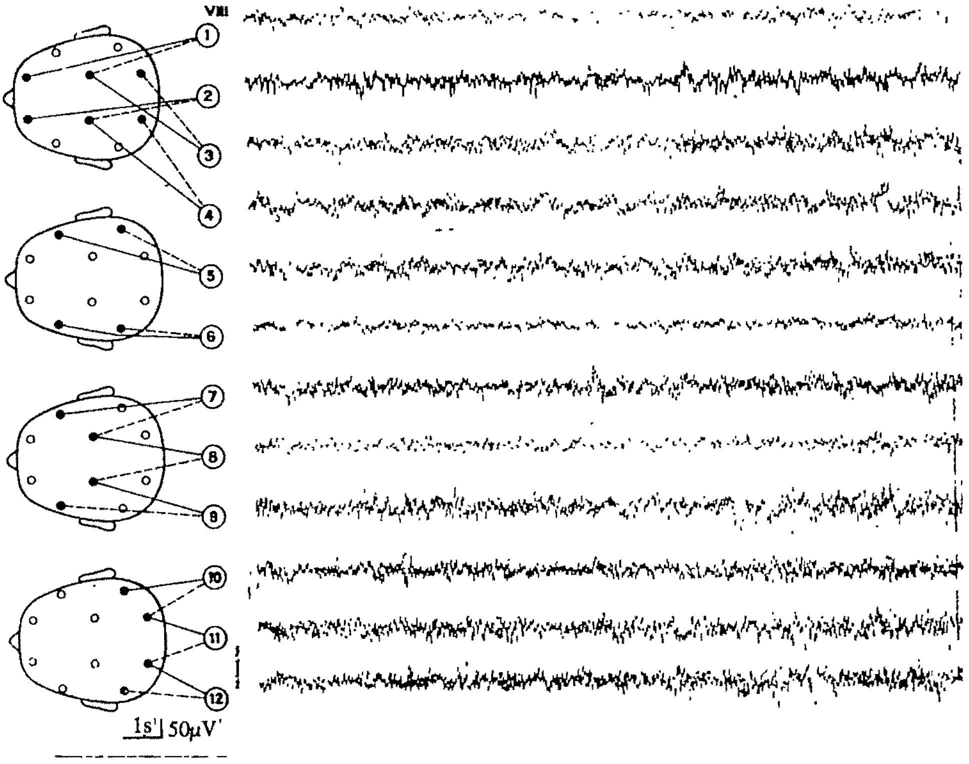

FIG. 2. *Case 5.* EEG displaying high amplitude fast rhythms at 14 to 22 Hz. Child awake.

spheroids were of variable size. Some were homogeneously stained. Others contained optically empty slits. On electron microscopy, the spheroids were seen to lie within terminal axons. They were composed of many membraneous and branching tubular profiles surrounded by a single membrane.

Case 6. L.G., the first child of French non-consanguineous parents, developed normally until he was 14 months old, although he was then unable to stand alone. At the age of 17 months, he had gross kyphosis in the sitting position, a lack of facial expression and some muscular wasting of the lower limbs. Deep tendon reflexes were normal. A Rossolimo sign was elicited bilaterally but the plantar reflexes were flexor. At the age of 26 months, he was extremely hypotonic and bilateral pyramidal signs were evident. Ocular movements were full and the optic discs were slightly pale. At 3 years 4 months marked amyotrophy was present and there were no spontaneous movements of the limbs. The feet tended to become fixed in the equinus position and some spasticity was also noted in the upper limbs. At 4 years of age, he was entirely helpless and blind. Painful stimulation elicited paroxysms of decerebrate rigidity. Both optic discs were atrophic. The CSF was repeatedly normal. The EEG consisted of high amplitude fast rhythms of 22 Hz, with a few interspersed spikes and slow waves. Denervation atrophy was shown by electromyography, fibrillation potentials were numerous.

Motor nerve conduction velocity was normal. The electroretinogram was normal but no visual evoked response could be elicited. Cortical biopsy showed numerous spheroids with the same structure as in Case 4, at both light and electron microscopy.

Case 7. A Tunisian girl (the sister of Case 8) born normally to healthy consanguineous parents who were first cousins once removed. She developed normally until the age of 12 months. At that time she stopped making progress and was never able to walk without assistance although she could move by holding on to furniture. Shortly afterwards, small amplitude ocular jerks were noted by the parents. When examined, at the age of 17 months, she was a very calm girl with a rather expressionless face and poor motor activity. Truncal and limb hypotonia was evident; she could no longer stand and exhibited a marked kyphosis when sitting. The deep tendon reflexes were exaggerated throughout and bilateral Rossolimo and Babinski reflexes were easily elicited. Unsustained ankle clonus was present. Head circumference was normal. She could see and follow moving objects, but gross pendular nystagmus was evident in the primary position, converting to jerk nystagmus when looking to either side. Fundi were questionably pale temporally. The CSF contained no cells, and 10 mg protein/dl. Pneumoencephalography disclosed no abnormality but the fourth ventricle and the supracerebellar cistern were poorly visualized. Arylsulphatases A and B were present in normal amounts in the urine. The EEG showed a mild excess of low amplitude fast rhythms in wakefulness and in sleep. Electromyography disclosed a neurogenic pattern of mild degree in the right tibialis anticus and the left common toe extensor. Motor conduction velocity in the left popliteal nerve was 47 m s^{-1} (normal). Neuromuscular biopsy was unremarkable by light microscopy. By electron microscopy a few degenerated axons were seen. At one point branched tubulovesicular structures were seen, apparently surrounded by a peri-axonal membrane. No specific diagnosis was made at that time.

After discharge from the hospital she deteriorated steadily. At the age of 2½ years, she was blind, hypotonic and bedridden. She died at home from bronchopneumonia. No autopsy was done.

Case 8. A boy, brother of Case 7. Two unaffected siblings were born in between. This was a dizygotic twin pregnancy. The second twin died at birth following a difficult and unattended delivery. Development seemed entirely normal until the age of 13 months, when the child was walking with assistance and uttering repeated syllables. From then on, no further progress was made and a slow deterioration was later observed. At the age of 19 months he was unable to stand and by 2 years of age he was unable to sit. A convergent strabismus became apparent, as well as a small amplitude pendular nystagmus. When examined, at the age of 24 months, gross hypotonia was evident and spontaneous movements were feeble. Deep tendon reflexes were exaggerated throughout and there were positive Babinski and Rossolimo signs. Head circumference was normal. The temporal sector of both optic discs was definitely pale. He reacted to painful stimuli. CSF examination including protein electrophoresis gave normal results (total protein 10 mg/dl). CT scan was normal without hypodense areas. The fourth ventricle did not appear enlarged. The electroretinogram was normal, as were the visual evoked responses. No deficit in lysosomal enzymes in leukocytes was detected. The EEG displayed a slight excess of low amplitude fast activity. Electromyography on right tibialis anticus, right peroneus longus, quadriceps, psoas, biceps and radial muscles was normal, except for an equivocal neurogenic pattern in the quadriceps. Motor conduction velocity was within normal limits in the right popliteal and median nerves (44 m s^{-1} and 43 m s^{-1}). Electron microscopic examination of a conjunctival biopsy showed typical spheroids.

REVIEW OF THE LITERATURE

Among 77 cases of infantile neuroaxonal dystrophy reviewed, 42 were selected on the following bases: (1) all had acceptable pathological evidence, either obtained at autopsy or by the demonstration of spheroids at biopsy of central or peripheral nervous tissue; (2) they fulfilled the following clinical criteria: (*a*) the onset of the disorder was before three years of age; (*b*) the clinical profile was one of diffuse disorder of the central nervous system, with psychomotor deterioration and increasing neurological involvement comprising symmetrical pyramidal tract signs and marked hypotonia; (*c*) the course was relentlessly progressive; (*d*) epileptic seizures, myoclonic jerks and extrapyramidal signs were not early or prominent features. Additional clinical and neurophysiological findings such as visual disturbances, evidence of peripheral nervous system involvement of an anterior horn cell type or EEG abnormalities (*see below*) were regarded as supporting diagnosis but not as necessary criteria for selection.

The above criteria were selected on the observation that among reported cases of INAD, two general groups could be recognized. The first and larger one, comprising those cases which satisfied the above clinical criteria, presented with a consistent clinical profile and course and appeared quite homogeneous. On the contrary, patients in the second group exhibited variable, seemingly unrelated, clinical pictures and appeared to constitute a heterogeneous collection of cases. In some of these latter cases certain pathological features were noted additional to the characteristic ones.

The 42 cases selected, together with the 8 cases presented here, are summarized in the Table. In these 50 cases the pathological evidence was obtained at post-mortem examination in 21. In 24, it was based on the finding of spheroid bodies by cortical biopsy (11 cases) or peripheral nerve biopsy (13 cases). Five patients not submitted to biopsy were diagnosed because verified cases of the disease had occurred in the same sibships.

Twenty-seven reported cases with the typical pathological features of the disease or belonging to sibships with at least one verified case were excluded since they did not conform to our arbitrary clinical criteria.

In eleven of these cases symptoms began before the age of 7 months and can be classified as the early infantile variety of neuroaxonal dystrophy (Crome and Weller, 1965, Cases 1 and 2; Jellinger, Seitelberger and Rosenkranz, 1968; Kamoshita, Neustein and Landing, 1968; Indravasu and Dexter, 1968, 4 cases; Richter, 1972; Scheffner, Feist, Kolkmann and Wille, 1973, 2 cases). All had early and prominent epileptic manifestations in the form of generalized seizures, myoclonic jerks or infantile spasms. In several cases the progressive nature of the disorder was not obvious (Jellinger *et al.*, 1968; Kamoshita *et al.*, 1968; Indravasu and Dexter, 1968, Case 4). In 2 patients, the disease commenced within two weeks of an immunization (Indravasu and Dexter, 1968, Case 1; Richter, 1972) and in one it followed a severe bout of pertussis (Indravasu and Dexter, 1968, Case 4) so that an acute encephalopathy is possible. Unusual pathological findings were present in at least 2 cases, e.g. diffuse sclerosis of the white matter (Crome and Weller, 1965, Case 2) and status marmoratus of the basal ganglia (Kamoshita *et al.*, 1968). These early infantile cases probably represent several different disorders.

Four cases of neuroaxonal dystrophy of late onset were clearly different from the cases considered here since, in addition to their late occurrence, they had a very protracted course with rigidity, cerebellar signs, intention tremor and myoclonus as the main features and with only slow mental deterioration (Rozdilsky, Bolton and Takeda, 1971; Thibault, 1972; Dorfman, Pedley, Tharp and Scheithauer, 1978). The pathological picture may be indistinguishable from that of the late infantile form (Scheithauer, Forno, Dorfman and Kane, 1978).

The cases of Gross, Kaltenback and Uiberrak (1957), of Rabinowicz and Wildi (1957) of Nakai, Landing and Schubert (1960) and of Brucher *et al.* (1968) also had their onset at 3 years of age or more and were therefore excluded. In the first of these cases the early development had been delayed and there was no visual disturbance, while in the third and fourth ataxia, ptosis and tapetoretinal degeneration were recorded.

The patient reported by Seitelberger, Gootz and Gross (1963) had a delayed early development, no hypotonia and the onset followed an acute febrile illness. Status dysmyelinatus was found at autopsy and no system atrophies were noted. The cases of Gilman and Barrett (1973) were excluded on account of the prominence of extrapyramidal signs and abnormal movements and that of Badurska, Jezierska, Prot and Rafalowska (1968) because of microcephaly. In the latter, motor conduction velocity was markedly slowed in the lower limbs.

The 2 siblings reported by Lyon and Sée (1963) were not retained as the clinical signs were predominantly cerebellar and pyramidal without hypotonia, and visual involvement was minimal. Similarly, the 2 familial cases of Yagishita and Kimura (1974) have been considered atypical because of the early occurrence of epileptic seizures and myoclonus and of the marked precocious rigidity. Spheroids were not found in the cerebral cortex in these cases.

Finally, another 8 cases have been excluded for want of sufficient pathological or clinical data (Seitelberger, 1952, 1953; Gonatas and Goldensohn, 1965; Duncan *et al.*, 1970, Cases 5, 6 and 7; De Coster, Roels and Vander Eecken, 1971; Ferriss, Happel and Duncan, 1977, Case 3).

These exclusions, clearly, are arbitrary but they seem justified since our aim has been to delineate a recognizable clinical picture rather than to define the nosological limits of the disease. The latter task will only become possible when more is known about its pathophysiology. A few of the cases retained exhibited deviations from the accepted clinical profile. Thus, hypotonia was not specifically mentioned in occasional cases (Toga, Bérard-Badier and Gambarelli-Dubois, 1970, Case 1; Haberland, Brunngraber and Witting, 1972; Yaghishita and Kimura, 1975). Visual failure was lacking or was not mentioned in 3 cases (Duncan *et al.*, 1970, Case 1; Kohn, Mundel and Wallis, 1970, Case 1; Ametani, 1974). Early seizures, before

TABLE. REPORTED CASES OF INFANTILE NEUROAXONAL DYSTROPHY FULFILLING THE CRITERIA SET FORTH IN THE PRESENT WORK

Authors	*Sex*	*Age at onset*	*Family history*	*Initial symptom*	*Psychomotor deterioration*	*Hypotonia*	*Visual disorder*	*Neurological course*	*Seizures*	*Confirmation of diagnosis*
Seitelberger (1952, 1953)	F	2 y	Affected monozygotic twin	Gait disturbance	+	+	+ Amaurosis	Spasticity, dementia, extensor spasms	±	Autopsy
Cowen and Olmstead (1963)										
Case 1	M	1 y 6 mo	+ (Sib Case 2)	Gait disturbance	+	+	+	Tetraparesis, hyporeflexia, swallowing difficulties	–	Autopsy
Case 2	F	1 y 3 mo	+ (Sib Case 1)	Gait disturbance	+	+	+	Areflexia, sensory impairment, contractures	–	Autopsy
Sandbank (1965)	M	1 y	–	Gait disturbance	+	+	+	Areflexia, hypotonia	–	Autopsy
Takei (1965)	M	1 y 2 mo	Consanguinity	Gait disturbance	+	+	+	Hypotonia, increased DTR spasticity, contractures	+	Autopsy
Huttenlocher and Gilles (1967)										
Case 1	F	8 mo	+ (Sib Cases 2, 3)	Slowing of development		+	+	Hyperreflexia, sensory impairment, contractures	–	Autopsy
Case 2	F	1 y	+ (Sib Cases 1, 3)	Arrest of development	+	+	+	Hyporeflexia, sensory impairment, contractures	–	Family history
Case 3	F	8 mo	+ (Sib Cases 1, 2)	Slowing of development	+	+	+	Hypotonia, pyramidal signs, sensory impairment	–	Family history
Gonatas *et al.* (1967)	M	1 y	–	Arrest of development	+	+	+ Nystagmus	Hypotonia, proximal spasticity, hyperreflexia, sensory impairment	+	Cortical biopsy
Herman *et al* (1969)	F	9 mo	–	Arrest of development	+	+	+ Nystagmus OA	Hyperreflexia, sensory impairment, contractures	–	Cortical biopsy
Rizzuto *et al.* (1969)										
Case 1	F	1 y 3 mo	+ (Sib Cases 2, 3, 4)	Arrest of development	+	+	+ Amaurosis	Hyperreflexia, spastic tetraplegia	–	Family history
Case 2	F	1 y	+ (Sib Cases 1, 3, 4)	Arrested development	+	+	+ Amaurosis	Spastic tetraplegia, contractures in flexion, amyotrophy	–	Autopsy
Case 3	M	1 y 2 mo	+ (Sib Cases 1, 2, 4)	Hypotonia	+	+	+ Amaurosis	Hyperreflexia, flaccid tetraplegia, amimia, abnormal movements	–	Autopsy
Case 4	F	1 y 2 mo	+ (Sib Cases 1, 2, 3)	Arrested development	+	+	+ Amaurosis	Pyramidal tract signs, generalized flaccidity	–	Family history
Sandbank, Lerman and Gelfman (1970)	F	11 mo	Consanguinity	Gait disturbance	+	+	+	Dementia, hyperreflexia, spasticity	–	Cortical biopsy
Duncan *et al.* (1970)										
Case 1	M	2nd y	+ (Sib Case 2)	Arrested development	+	+	?	Areflexia, amyotrophy, flaccidity then contractures	+ late	Autopsy
Case 2	M	8 mo	+ (Sib Case 1)	Arrested development	+	+	+ Late OA	Hyperreflexia, impaired sensitivity	–	Nerve biopsy
Case 3	F	1 y 6 mo	+ (1 affected brother)	Slowing of development	+	+	+ Strabismus	Hypotonia, hyporeflexia, dementia	–	Nerve biopsy
Case 4	F	1 y	–	Gait disturbance	+	+	+ OA	Hyporeflexia, amyotrophy, amimia	–	Nerve biopsy
Toga *et al.* (1970)										
Case 1	M	1 y 6 mo	Consanguinity	Gait disturbance	+	?	+	Spasticity, contractures	–	Autopsy
Case 2	F	1 y 1 mo	–	Arrested development	+	+	+	Pyramidal tract signs, paraparesis	–	Cortical biopsy
Kohn *et al.* (1970)										
Case 1	F	1 y 6 mo	Consanguinity	Arrested development	+	+	–	Pyramidal tract signs, dystonic spasms, choreoathetoid movements	+	Autopsy
Case 2	M	1 y	+ 2 affected sibs, consanguinity	Arrested development	+	+	+	Hyperreflexia, hypertonia upper limbs	–	Autopsy
Case 3	M	1 y 4 mo	+ (Sib Cases 2, 4)	Arrested development	+	+	+	Hypotonia, hyporeflexia, sensory impairment, contractures	–	Autopsy
Case 4	F	1 y 2 mo	+ (Sib Cases 2, 3)	Arrested development	+	+	+	Hyporeflexia, amyotrophy	–	Autopsy
Haberland *et al.* (1972)	F	1 y	–	Gait disturbance, seizures	+	+	+ OA	Hyporeflexia, sensory impairment	+	Autopsy

Martin *et al.* (1972)										
Case 1	F	1 y	+ (Sib Case 2)	Arrested development	+	+	+	Dementia, mixed hypo- and hypertonia, spasticity	–	Autopsy
Case 2	M	1 y	+ (Sib Case 1)	Gait disturbance	+	+	+	Flaccidity then spasticity, hyporeflexia	–	Autopsy
Case 3	M	6 mo	–	Hypotonia	+	+	+ Amaurosis	Hypotonia, proximal spasticity, decerebration	–	Cortical biopsy
Case 4	F	1 y	Consanguinity (double)	Psychomotor regression	+	+	+	Hypotonia, proximal spasticity, hyperreflexia	–	Cortical biopsy
Sengel and Stoebner (1972)										
Case 2	F	1 y	+ (Sib Case 3)	Psychomotor regression	+	+	+ OA	Pyramidal signs, dementia, hyperreflexia	–	Neuromuscular biopsy
Case 3	M	1 y 2 mo	+ (Sib Case 2)	Psychomotor regression	+	+	+ Strabismus	Pyramidal signs, dementia	–	Neuromuscular biopsy
Rizzuto, Vio, Gherdini and Panizon (1973)	M	1 y 3 mo	+ (1 affected brother)	Slowing of development	+	+	+ Amaurosis	Flaccid tetraparesis, hyperreflexia, rhythmic motions of head	–	Autopsy
Mei Liu *et al.* (1974)	F	1 y	–	Gait disturbance	+	+	+	Hypotonia, pyramidal tract signs, sensory impairment	–	Cortical biopsy
Ametani (1964)	M	1 y	+ (1 affected sister)	Arrest of development	+	+	–	Dementia, amyotrophy, flexion contractures	–	Autopsy
Onnis, Nardelli, Buonanno, Galliazzo-Rizzuto, Panizon and Rizzuto	M	1 y	+ (1 affected brother)	Psychomotor regression	+	+	+ OA	Flaccid, then spastic tetraplegia	–	Autopsy
Yagishita and Kimura (1975)	M	1 y 4 mo	–	Arrest of development	+	?	+	Rigidity, involuntary movements, pyramidal tract signs	+ (late)	Autopsy
Juif *et al.* (1975)										
Case 3	F	1 y	+ (3 affected sibs)	Arrest of development	+	+	+	Hyperreflexia, pyramidal tract signs, contractures	–	Cortical biopsy
Shimono *et al* (1976)	M	1 y 3 mo	–	Arrest of development	+	+	+ OA	Hypotonia, proximal spasticity, extensor spasms	–	Nerve biopsy
Ferriss *et al.* (1977)										
Case 1	M	1 y 7 mo	–	Psychomotor regression	+	+	+ Nystagmus	Hypotonia, muscle atrophy, tonic spasms	–	Neuromuscular biopsy
Case 2	F	1 y 3 mo	+	Arrest of development	+	+	?	Hypotonia, pyramidal tract signs, amyotrophy	–	Nerve biopsy
Yagishita *et al.* (1978)	M	8 mo	–	Nystagmus, regression	+	+	?	Pyramidal tract signs, amimia	–	Nerve biopsy
Present series										
Case 1	M	1 y	–	Psychomotor regression	+	+	+ OA	Pyramidal tract signs, amyotrophy, extensor spasms	–	Cortical biopsy
Case 2	F	1 y 4 mo	–	Arrest of development	+	+	+ OA	Pyramidal tract signs, dementia	–	Skin and conjunctival biopsy*
Case 3	M	11 mo	–	Arrest of development	+	+	+ Nystagmus	Dementia, amyotrophy, pyramidal tract signs	–	Skin and conjunctival biopsy*
Case 4	M	1 y 2 mo	Consanguinity (double)	Psychomotor regression	+	+	+ Nystagmus	Pyramidal tract signs, muscle wasting	–	Skin and conjunctival biopsy
Case 5	F	11 mo	–	Psychomotor regression	+	+	+	Exaggerated DTR, amimia, muscle wasting	–	Cortical biopsy
Case 6	M	1 y 2 mo	–	Psychomotor regression	+	+	+ OA	Flaccid, then spastic quadriplegia, decerebrate rigidity	–	Cortical biopsy
Case 7	F	1 y	+ (Sister of Case 8)	Slowing of development	+	+	+ Nystagmus OA	Quadriplegia, dementia, blindness, died at 2½ y	–	Family history
Case 8	M	1 y	+ (Brother of Case 7) consanguinity	Slowing of development	+	+	+ Nystagmus	At 2 years, hypotonia, pyramidal syndrome, mental regression	–	Conjunctival biopsy

DTR = deep tendon reflexes. OA = optic atrophy. * = conjunctival biopsy findings have been published by Arsenio-Nunes and Goutières (1978)

2 years of age, occurred in 3 patients (Takei, 1965; Gonatas, Evangelista and Walsh, 1967; Kohn *et al.*, 1970). These atypical features were neglected when all other pathological and clinical evidence was compatible with infantile neuroaxonal dystrophy.

With these reservations, the following clinical picture emerges from the analysis of these 50 cases.

The onset was between the age of 6 months and 2 years in all cases and between 10 months and 2 years in 42. The initial symptom was a slowing of the rate of motor and mental development, followed by a definite regression with loss of previously acquired milestones. This was often a slow process and, in several cases, a firm diagnosis of a progressive disorder could not be made until a few months had elapsed. Psychomotor regression was associated with the appearance of increasing hypotonia and, sometimes, with muscular weakness of such a degree as to suggest a diagnosis of myopathy or of spinal muscular atrophy (Cases 1 and 3 in the present series). Within a few months, walking, standing and sitting abilities were lost and movements of the limbs, especially the lower ones, became feeble. The elements of speech already acquired progressively disappeared. Pyramidal tract signs were regularly present with extensor plantar responses (which may not exist early as in our Cases 4 and 5) and, in a majority of the cases, exaggerated deep tendon reflexes. Muscle atrophy was noted in some infants, reflecting involvement of the lower motor neuron. This may have been responsible for the loss or diminution of deep tendon reflexes found in at least 11 cases (Cowen and Olmstead, 1963, Case 2; Sandbank, 1965; Takei, 1965; Huttenlocher and Gilles, 1967, Case 2; Duncan *et al.*, 1970, Cases 1 and 3; Kohn *et al.*, 1970, Case 3; Martin *et al.*, 1972, Case 1; Mei Liu, Larson and Mizuno, 1974; present series Cases 1 and 3). Visual symptoms and signs, including strabismus, pendular nystagmus, incoordinate eye movements and failing vision were generally early and prominent. Optic atrophy was mentioned in 40 per cent of the Cases by the age of 3 years and in a further 30 per cent by the age of 3½ years. Sensory abnormalities, mainly expressed as limited reaction to pinprick and occasionally to touch, were repeatedly reported (Cowen and Olmstead, 1963; Huttenlocher and Gilles, 1967, Cases 2 and 3; Gonatas *et al.*, 1967; Herman, Huttenlocher and Bensch, 1969; Duncan *et al.*, 1970, Case2; Kohn *et al.*, 1970, Case 3; Haberland *et al.*, 1972; Mei Liu *et al.*, 1974), but these may be difficult to detect in young or demented patients.

A regular unremitting course was observed in all cases. Interestingly, spasticity may replace hypotonia, often with a proximal onset (Martin *et al.*, 1972). A decorticate state finally obtains, with re-emergence of primitive reflexes and appearance of abnormal reactions to external stimuli, comprising diffuse, complex automatic movements. Seizures are rare. They were reported in 11 patients and were usually a late event. In at least a proportion of the cases, they may have been non-epileptic in nature, since paroxysms of opisthotonus or of decerebrate rigidity were common and can mimic epileptic fits (Ferris *et al.*, 1977). Extrapyramidal signs were only rarely described (Seitelberger, 1952; Kohn *et al.*, 1970; Yagishita and Kimura, 1975).

Terminally, bulbar signs, for example difficulty with swallowing, dyspnœa, and sphincter disturbances may supervene. At this stage, the patients are totally helpless, blind, tetraplegic and demented. The total duration of the disease did not exceed ten years when the age of death was known, except in Case 2 of Cowen and Olmstead, who was still alive after 12 years at the time of their report. The mean duration was about 5 years, and death had occurred by 4 years in 40 per cent of the reported cases.

Laboratory investigations provide important diagnostic clues. A normal CSF was found in all cases except in the patient of Toga *et al.* (1970) who had a protein level of 40 mg per cent. Electrophoresis of the CSF in all our cases showed a normal protein pattern. Lysosomal enzymes in leucocytes were also normal in all patients studied. Slightly or moderately raised levels of glutamic oxaloacetic transaminase and lactic dehydrogenase have been reported both in CSF and blood (Huttenlocher and Gilles, 1967; Kohn *et al.*, 1970; Duncan *et al.*, 1970; Martin *et al.*, 1972; Shimono *et al.*, 1976) but are both inconstant and non-specific. Neurophysiological studies may also aid the clinical diagnosis of infantile neuroaxonal dystrophy. The presence of high amplitude, non-reactive, fast rhythms at 16 to 22 Hz in the EEG both in sleep and in the waking state (fig. 1) was first mentioned by Radermecker and Martin (1972). Recently Ferriss *et al.* (1977) made a detailed study of these rhythms. According to these workers, they were never encountered before the age of 2 years and may even appear between 3 and 5 years. Fast rhythms were specifically reported between the ages of 2 and 3 years in at least 14 of 25 patients studied (Huttenlocher and Gilles, 1967, 3 cases; Radermecker and Martin, 1972, 3 cases; Mei Liu *et al.*, 1974; Ferriss *et al.*, 1977, 2 cases; present report, Cases 2, 3, 4, 5 and 6) and were probably present in at least 4 further cases (Sandbank, 1965; Takei, 1965; Hermann *et al.*, 1969; Duncan *et al.*, 1970). High voltage fast rhythms were already present at the age of 23 months in our Case 5. They were absent at ages 21 and 19 months, respectively, in our Cases 2 and 4, but were obvious in the same patients at 33 and 26 months of age. Although this abnormal EEG activity is not specific for infantile neuroaxonal dystrophy (Ferriss *et al.*, 1977) it is highly suggestive in an appropriate clinical setting. Other EEG abnormalities, for example, spikes, isolated or in bursts, and slow waves are frequently mentioned and seem to increase with advancing age, but these have no particular diagnostic value. The frequent occurrence of electromyographic signs of denervation of the type observed in anterior horn lesions is noteworthy. They have been found in at least 22 patients and were usually present by the age of 2 to 3 years (Sandbank, 1965; Takei, 1965; Huttenlocher and Gilles, 1967, 3 cases; Gonatas *et al.*, 1967; Rizzuto, Dalla Barba, Bonan, Rebeschini and Amaducci, 1969, Case 3; Duncan *et al.*, 1970, Case 2; Kohn *et al.*, 1970, Case 2; Martin *et al.*, 1972, Case 4; Sengel and Stoebner, 1972; Rizzuto, Vio, Ghersini and Panizon 1973; Mei Liu *et al.*, 1974; Juif, Isch, Lausecker, Heldt and Churlet, 1975; Ferriss *et al.*, 1977, Cases 1 and 2; present report, Cases 1, 3, 4, 5 and 7). Motor conduction velocity was normal in all cases studied except in the patient of Juif *et al.* (1975) in whom it was 28 ms^{-1}. Sensory conduction velocity was measured in only a few patients (Martin *et al.*, 1972; Shimono *et al.*, 1976; present series Case 1) and was within normal limits. The electroretinogram was unremarkable in the few cases in which it was recorded. Visual evoked responses were reported to be abnormal by Ferriss *et al.* (1977), a finding they interpreted as indicating cortical isolation, together with the unreactive, fast rhythms in the EEG. The visual evoked responses, however, were normal in Cases 1, 3 and 8 of the present series, present but of a markedly reduced amplitude in Cases 2 and 8 and totally lacking in Cases 4, 5 and 6. In Case 4, the latency of the somæsthetic evoked response was increased and an abnormal configuration was seen. Thus the presence of a normal visual evoked response cannot be taken as evidence against the diagnosis of infantile neuroaxonal dystrophy.

The clinical diagnosis of infantile neuroaxonal dystrophy was confirmed by a variety of pathological means, as shown in the Table. It is not the purpose of this paper to review the pathological findings, which have been extensively discussed previously. The diagnostic value of peripheral biopsies will be discussed below.

Infantile neuroaxonal dystrophy, in the restricted sense accepted in this work, is frequently a familial disorder. Eighteen reported cases belonged to 7 sibships with 2 to 4 affected members. Affected siblings were mentioned without details in another 5 cases. Seitelberger's initial patient was one of a pair of affected twins. Case 2 of Ferriss *et al.* (1977) was a half-sibling of Cases 1 and 2 of Duncan *et al.* (1970). According to Juif *et al.* (1975), the distribution of patients in published families is compatible with a recessive autosomal inheritance. In 21 sibships, they found 33 affected children out of a total of 86 offspring. The high incidence of consanguinity, found in 8 families (Takei, 1965; Sandbank, 1965; Toga *et al.*, 1970; Kohn *et al.*, 1970; Martin *et al.*, 1972; present report, Cases 4, 7 and 8) also supports this hypothesis. Interestingly, all published familial cases displayed a closely similar clinical picture and no cases with significantly different age of onset within a sibship are on record.

DISCUSSION

The diagnosis of infantile neuroaxonal dystrophy is classically based on a constellation of neuropathological findings (Cowen and Olmstead, 1963; Martin *et al.*, 1972). This pathological picture may be associated with different clinical profiles and occurs in different age groups. With this approach diagnosis during life is clearly impossible, since no single pathological feature (especially the presence of spheroids in axons) is specific.

The recognition of a clinical syndrome that is highly suggestive of one major form of infantile neuroaxonal dystrophy, the late infantile one, particularly when spheroid bodies have been regularly demonstrated in such cases in cortical biopsies or in the axons of peripheral nerves, provides an opportunity of recognizing the disorder during life. A combined approach, using both the clinical profile and the finding of spheroids at biopsy is, however, necessary, since neither the clinical nor the biopsy findings can be entirely relied upon at this time, for reasons discussed below.

In fact, the majority of recently published reports of late infantile neuroaxonal dystrophy are of cases which did not come to autopsy, diagnosed by combined clinicopathological means (Herman *et al.*, 1969; Sandbank *et al.*, 1970; Duncan *et al.*, 1970; Toga *et al.*, 1970; Martin *et al.*, 1972; Sengel and Stoebner, 1972; Mei Liu *et al.*, 1974; Juif *et al.*, 1975; Shimono *et al.*, 1976; Yagishita, Itoh, Nakano, Oizumi, Okuyama and Aoki, 1978). The diagnosis of this disease in our 8 patients thus appears justified according to present trends even though none of them came to autopsy. Their clinical presentation was typical and the spheroids demonstrated in the cortex in 3 cases and in the skin and conjunctiva in 4 others had a fine structure identical to that described by Gonatas *et al.* (1967), Hedley-White, Gilles and Uzman (1968), Herman *et al.* (1969), Toga *et al.* (1970), Sandbank *et al.* (1970) and Martin *et al.* (1972).

The current acceptance of the diagnosis of infantile neuroaxonal dystrophy in patients who did not come to autopsy reflects an interesting modification in the nosological concept of the condition. This concept has evolved from that of a disorder defined essentially in neuropathological terms to that of a recognizable disease, characterized by a definite clinical and neurophysiological picture, in association with the finding of spheroids in central and, more recently, peripheral nervous tissues.

The evidence that the presence of spheroids in the cerebral cortex or in peripheral axons is diagnostic of infantile neuroaxonal dystrophy, however, is far from complete. In only 4 cases (Toga *et al.*, 1970, Cases 1 and 2; Martin *et al.*, 1972, Case 3; Juif *et al.*, 1975, Case 3) has a diagnosis made by cortical biopsy been confirmed at autopsy. Likewise, the correlation between the presence of spheroids in peripheral axons and in cortical biopsy specimens seems to have been verified in only 3 cases (Berard-Badier *et al.*, 1971; Martin and Martin, 1972; Sengel and Stoebner, 1972). Thus, the arguments which support the diagnostic validity of biopsy, whether central or peripheral, are mainly indirect ones: (1) the fine structure of the spheroids is identical in the peripheral nervous system, in the cortex and in other parts of the central nervous system; (2) the spheroids have rarely been found in cortical biopsies from patients suffering from disorders other than infantile neuroaxonal dystrophy, although Dooling, Schoene and Richardson (1974) reported their presence in cortical biopsies from patients with Hallervorden-Spatz disease; (3) they have never been found, so far, in peripheral nerves or in nerve endings of a large number of patients suffering from a variety of degenerative disorders of the central nervous system. Thus, J. Libert (personal communication, 1977) has not encountered spheroids in several hundred conjunctival biopsies, nor has Arsenio-Nunes in 130 skin and 50 conjunctival biopsies, performed for the diagnosis of progressive disorders of the central nervous system in children (unpublished results). Interestingly, no spheroids were found in the peripheral (end-plate) biopsy of one patient with the so-called early infantile neuroaxonal dystrophy verified at autopsy (Mancini-Mellan, 1978).

Much more data is therefore needed before it can be confidently stated that the finding of spheroids in peripheral nerve endings is consistently associated with, and characteristic of, late infantile neuroaxonal dystrophy. Pending such demonstration, we believe that the evidence favouring the diagnostic value of peripheral biopsy is impressive, although admittedly not absolute, and we should be reluctant to accept a diagnosis of the disease on purely clinical grounds.

The striking constellation of clinical and neurophysiological abnormalities outlined above makes the differential diagnosis of the disease from other known degenerative disorders in the same age range relatively easy. We found that the most useful clues were the profound hypotonia, of a degree rarely encountered in other progressive cerebral disorders, the early visual involvement and the lack of seizure activity. The normal CSF protein level is an important negative finding. The frequent occurrence of electromyographic signs of denervation with normal conduction velocity is of special diagnostic importance since it is seldom, if ever, observed in central progressive disorders of infants. The presence of high voltage fast rhythms in the EEG and the association of a normal electroretinogram with absent or reduced visual evoked responses are also helpful in distinguishing this disease from other degenerative disorders.

Metachromatic leucodystrophy, which more closely mimics infantile neuroaxonal dystrophy, can be ruled out by the absence of hyperproteinorrachia, normal nerve conduction velocities and by enzymatic studies in leucocytes or fibroblasts. The various types of gangliosidosis, especially the late form of GM_1 gangliosidosis can similarly be excluded. The absence of seizures and myoclonus, the normal electroretinogram and the different EEG abnormalities make the distinction between infantile neuroaxonal dystrophy and the so-called ceroid lipofuscinoses an easy one. Leigh's subacute encephalomyelopathy often begins at the same age, can feature early hypotonia and optic atrophy and, in consequence, may cause serious diagnostic problems. The neurophysiological abnormalities consistently seen in infantile neuroaxonal dystrophy have not been recorded, however, in this disorder, nor have the biochemical abnormalities sometimes found in Leigh's encephalopathy been reported in infantile neuroaxonal dystrophy. Another diagnostic difficulty encountered in this series was to distinguish the early stages of the disease from a static neurological condition because of the initially very slow progression of the disorder. Several months may elapse before the progressive course of the disease can be recognized. Finally it is clear that several, as yet undefined, progressive disorders of the central nervous system occur in infancy and early childhood, and that at least some of them may resemble infantile neuroaxonal dystrophy. This is, in our view, an important reason for not accepting the diagnosis without pathological evidence.

Difficulties may also arise at the neuropathological stage of the diagnosis. Spheroids may not be seen by light microscopy in routine preparations, although they are clearly demonstrated in semi-thin and thin sections prepared for electron microscopy (Gonatas *et al.*, 1967; Herman *et al.*, 1969; Sandbank *et al.*, 1970; present report, Case 1). This should no longer constitute a problem if all cortical biopsies are now examined ultrastructurally and prepared accordingly. When peripheral biopsies are used, finding spheroids in axons may be a time consuming and tedious process, which is justified only when the diagnosis of infantile neuroaxonal dystrophy is strongly entertained clinically. As shown by Berard-Badier *et al.* (1971) and by Martin and Martin (1972), characteristic axonal dystrophy is found more easily and is more typical in terminal axons, such as those obtained by muscular end-plate biopsies, than in more proximal nerve fibres. The same seems to apply to cutaneous and conjunctival biopsies (Arsenio-Nunes and Goutières, 1978). Since biopsies of the skin or conjunctiva are quite simple to perform and can be obtained on outpatients, we now prefer them to neuromuscular biopsies.

The nosological situation of the disorder remains controversial and a definitive answer to the questions raised will have to await characterization of the fundamental defect underlying its manifestations.

A purely pathological definition of the disorder is, in our opinion, untenable. The non-specific character of the spheroids is well recognized, so that pathological diagnosis must rely on the more or less extensive distribution of the spheroids in the nervous system and on their association with other pathological features, for example, cerebellar atrophy, system degeneration, basal ganglia involvement and so on. These associated abnormalities, in turn, are not individually characteristic and only a complex of spheroids in a certain distribution and of other pathological features is considered acceptable evidence (Cowen and Olmstead, 1963; Martin *et al.*, 1972). There is no absolute agreement, however, as to precisely which topographical distribution of the spheroids and which associated neuropathological changes allow a diagnosis of infantile neuroaxonal dystrophy to be made in a particular patient. This is illustrated by the fact that the disorder was first considered an infantile variant of Hallervorden-Spatz disease (Seitelberger, 1952, 1953; Seitelberger and Gross, 1957) and by the flurry of papers discussing the relationships between the two disorders (Bini, 1952; Sacks, Aguilar and Brown, 1966; Brucher *et al.*, 1968; Indravasu and Dexter, 1968; Seitelberger, 1971; Radermecker and Martin, 1972; Defendini *et al.*, 1973; Gilman and Barrett, 1973). Such features as the presence or absence of pigment in the basal ganglia are known to be non-discriminative and the wide distribution of the spheroids in the central nervous system, especially in the cortex, which is an important feature of infantile neuroaxonal dystrophy, has also been reported in Hallervorden-Spatz disease (Dooling *et al.*, 1974). Moreover, cases difficult to classify as either of these diseases are on record (Gross *et al.*, 1957; Seitelberger *et al.*, 1963). Even though only cases with a classical neuropathological picture are accepted, the corresponding clinical pictures and courses remain heterogenous. Such is the case with the early infantile types of NAD and, especially, with the late onset forms (Rozdilsky *et al.*, 1971; Thibault, 1972; Dorfman *et al.*, 1978) whose clinical expression is mainly one of intention tremor or myoclonus with a protracted course and very slow deterioration of intellectual functions. The pathological substratum of the juvenile cases is, however, identical with that of the infantile form (Scheithauer *et al.*, 1978).

On the contrary, the use of a definition combining both clinical and pathological (biopsy) criteria makes it possible to isolate a homogeneous group of cases which might be tentatively regarded as constituting a single, genetically determined, disorder transmitted by recessive autosomal inheritance and whose diagnosis is possible during life. In this regard, it is interesting to note that cases of infantile neuroaxonal dystrophy occurring within the same sibship always had the same presentation and that, to the best of our knowledge, there is no record of cases with different ages of onset or with markedly different clinical manifestations in the same family. We are fully aware that the condition we have studied, and which is not particularly rare since we were able to collect 8 cases over a five-year period, may represent only the more typical form of a disease with a broader clinical spectrum. We believe, however, that a restricted acceptance of the term infantile neuroaxonal dystrophy can serve a useful clarifying purpose, from the practical standpoints of diagnosis and genetic counselling.

SUMMARY

Eight cases of late infantile neuroaxonal dystrophy are reported. In all cases, the diagnosis was made during life on the basis of the clinical picture and course, the results of neurophysiological studies and the finding of typical spheroids in cortical or peripheral (skin and conjunctival) biopsies.

A review of 76 previously published cases revealed that 42 displayed a stereotyped clinical picture identical to that exhibited by our 8 patients.

The most important clinical features, as they emerge from the study of these 50 cases, are those of a progressive disorder starting at the end of the first or beginning of the second year of life, progressive motor and mental deterioration, bilateral pyramidal tract signs, marked hypotonia and early visual disturbances without epileptic seizures.

The presence of high voltage, fast rhythms in the EEG and signs of denervation of an anterior horn-cell type at EMG, with normal nerve conduction velocities, is frequent additional evidence in favour of infantile neuroaxonal dystrophy.

The finding of spheroid bodies in axonal endings seems to be constant and is necessary for an *in vivo* diagnosis. Spheroids can be found in peripheral tissues, for example, skin and conjunctiva, and cortical biopsy is no longer required. The spheroids, however, are not specific and both clinical and pathological features are necessary to establish a firm diagnosis.

Since infantile neuroaxonal dystrophy is a recessively inherited disorder its recognition is imperative even though the nosology of the disease remains uncertain.

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REFERENCES

AMETANI, T. (1974) Infantile neuroaxonal dystrophy. Light and electron microscopic observations of an autopsy case. *Neuropädiatrie*, **5**, 63–70.

ARSENIO-NUNES, M. L. and GOUTIÈRES, F. (1978) Diagnosis of infantile neuroaxonal dystrophy by conjunctival biopsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 511–515.

BADURSKA, B., JEZIERSKA, K., PROT, J. and RAFALOWSKA, J. (1968) A case of neuroaxonal dystrophy of Seitelberger recognized intravitally. *Polish Medical Journal*, **7**, 1209–1213.

BÉRARD-BADIER, M., GAMBARELLI, D., PINSARD, N., HASSOUN, J. and TOGA, M. (1971) Infantile neuroaxonal dystrophy or Seitelberger's disease. II. Peripheral nerve involvement: electron microscopic study in one case. *Acta Neuropathologica, Berlin*, Supplement 5, 30–39.

BINI, L. (1952) Sul valore dei reperti istopatologici per la nosografia della malattia di Hallervorden-Spatz. In: *Proceedings of the First International Congress of Neuropathology, Rome, 1956*. Torino: Rosenberg and Sellier, vol. 3, pp. 90–100.

BRUCHER, J. M., DOM, R. and ROBIN, A. (1968) Dégénérescence juvénile du système nerveux central. Ses rapports avec la maladie d'Hallervorden-Spatz et les dystrophies neuroaxonales. *Revue Neurologique, Paris*, **119**, 425–444.

COWEN, D. and OLMSTEAD, E. V. (1963) Infantile neuroaxonal dystrophy. *Journal of Neuropathology and Experimental Neurology*, **22**, 175–236.

CROME, L. and WELLER, S. D. V. (1965) Infantile neuroaxonal dystrophy. *Archives of Diseases in Childhood*, **40**, 502–507.

DE COSTER, W., ROELS, H. and VANDER EECKEN, H. (1971) Electron microscopical study of neuroaxonal dystrophy. *European Neurology*, **5**, 65–83.

DEFENDINI, R., MARKESBERY, W. R., MASTRY, A. R. and DUFFY, P. E. (1973) Hallervorden-Spatz disease and infantile neuroaxonal dystrophy. Ultrastructural observations, anatomical pathology and nosology. *Journal of the Neurological Sciences*, **20**, 7–23.

DOOLING, E., SCHOENE, W. and RICHARDSON, E. (1974) Hallervorden-Spatz syndrome. *Archives of Neurology, Chicago*, **30**, 70–83.

DORFMAN, L. J., PEDLEY, T. A., THARP, B. R. and SCHEITHAUER, B. W. (1978) Juvenile neuroaxonal dystrophy: clinical, electrophysiological and neuropathological features. *Annals of Neurology*, **3**, 419–428.

DUNCAN, C., STRUB, R., MCGARRY, P. and DUNCAN, D. (1970) Peripheral nerve biopsy as an aid to diagnosis in infantile neuroaxonal dystrophy. *Neurology, Minneapolis*, **20**, 1024–1032.

FERRISS, G. S., HAPPEL, L. T. and DUNCAN, M. C. (1977) Cerebral cortical isolation in infantile neuroaxonal dystrophy. *Electroencephalography and Clinical Neurophysiology*, **43**, 168–182.

GILMAN, S. and BARRETT, R. E. (1973) Hallervorden-Spatz disease and neuroaxonal dystrophy. Clinical characteristics and nosological considerations. *Journal of the Neurological Sciences*, **19**, 189–205.

GONATAS, N. K. and GOLDENSOHN, E. S. (1965) Unusual neocortical presynaptic terminals in a patient with convulsions, mental retardation and central blindness: an electron microscopic study. *Journal of Neuropathology and Experimental Neurology*, **24**, 539-562.

—— EVANGELISTA, I. and WALSH, G. O. (1967) Axonic and synaptic changes in a case of psychomotor retardation: an electron microscopic study. *Journal of Neuropathology and Experimental Neurology*, **26**, 179-199.

GROSS, H., KALTENBACK, E. and UIBERRAK, B. (1957) Über eine spät infantile Form der Hallervorden-Spatzschen Krankheit. 1. Klinisch-anatomische Befunde. *Deutsche Zeitschrift für Nervenkrankheiten*, **176**, 77-103.

HABERLAND, C., BRUNNGRABER, E. G. and WITTING, L. A. (1972) Infantile neuroaxonal dystrophy. *Archives of Neurology, Chicago*, **26**, 391-402.

HEDLEY-WHITE, E. T., GILLES, F. H. and UZMAN, B. (1968) Infantile neuroaxonal dystrophy: a disease characterized by altered terminal axons and synaptic endings. *Neurology, Minneapolis*, **18**, 891-906.

HERMAN, M. N., HUTTENLOCHER, P. R. and BENSCH, R. G. (1969) Electron microscopic observation in infantile neuroaxonal dystrophy. *Archives of Neurology, Chicago*, **20**, 19-33.

HUTTENLOCHER, P. R. and GILLES, F. H. (1967) Infantile neuroaxonal dystrophy. Clinical, pathologic and histochemical findings in a family with three affected siblings. *Neurology, Minneapolis*, **17**, 1174-1184.

INDRAVASU, S. and DEXTER, R. (1968) Infantile neuroaxonal dystrophy and its relationship to Hallervorden-Spatz disease. *Neurology, Minneapolis*, **18**, 693-699.

JELLINGER, K. and JIRASEK, A. (1971) Neuroaxonal dystrophy in man: character and natural history. *Acta Neuropathologica, Berlin*, Supplement 5, 3-16.

—— SEITELBERGER, F. and ROSENKRANZ, W. (1968) Infantile neuroaxonale Dystrophie. Frühform mit bevorzugtem Kleinhirnbefall. *Acta Neuropathologica, Berlin*, **10**, 123-131.

JUIF, J. G., ISCH, F., LAUSECKER, C., HELDT, N. and CHURLET, Y. (1975) La dystrophie neuroaxonale infantile ou maladie de Seitelberger. *Pédiatrie, Lyon*, **30**, 451-461.

KAMOSHITA, S., NEUSTEIN, H. B. and LANDING, B. H. (1968) Infantile neuroaxonal dystrophy with neonatal onset. Neuropathologic and electron microscopic observations. *Journal of Neuropathology and Experimental Neurology*, **27**, 300-323.

KOHN, R., MUNDEL, G. and WALLIS, K. (1970) Infantile neuroaxonal dystrophy. *Confinia Neurologica*, **32**, 409-422.

LAMPERT, P. W. (1967) A comparative study of reactive, degenerating, regenerating and dystrophic axons. *Journal of Neuropathology and Experimental Neurology*, **26**, 345-368.

—— and PENTSCHEW, A. (1964) An electron microscopic study of spheroids and convoluted bodies in dystrophic terminal axons. *Acta Neuropathologica, Berlin*, **4**, 158-168.

LYON, G. and SÉE, G. (1963) La dégénérescence neuroaxonale (maladie de Seitelberger). *Revue Neurologique, Paris*, **109**, 133-155.

MANCINI-MELLAN, J. (1978) *La Dystrophie Neuroaxonale Infantile*. Thèse Médècine, Marseille.

MARTIN, J. J. and MARTIN, L. (1972) Infantile neuroaxonal dystrophy. *European Neurology*, **8**, 239-250.

MARTIN, L., TRELLES, L. and MARTIN, J. J. (1972) Evolution clinique de la dystrophie neuro-axonale infantile à la lumière de la chronologie des atrophies systématisées sous-jacentes. *Journal of the Neurological Sciences*, **15**, 439-455.

MEI LIU, H. (1978) Reactive neuroaxonal dystrophy in children. Clinical pathological correlation. *Acta Neuropathologica, Berlin,* **42,** 237-241.

—— LARSON, M. and MIZUNO, Y. (1974) An analysis of the ultrastructural findings in infantile neuroaxonal dystrophy (Seitelberger's disease). *Acta Neuropathologica, Berlin,* **27,** 201-213.

NAKAI, H., LANDING, B. and SCHUBERT, W. (1960) Seitelberger's spastic amaurotic axonal idiocy. Report of a case in a 9-year-old boy with comment on visceral manifestations. *Pediatrics,* **25,** 441-449.

ONNIS, L., NARDELLI, E., BUONANNO, F., GALIAZZO-RIZZUTO, S., PANIZON, F. and RIZZUTO, N. (1975) La distrofia neuroaxonale infantile. Studio anatomoclinico di un caso. *Rivista di Patologia Nervosa e Mentale,* **96,** 322-339.

RABINOWICZ, T. and WILDI, E. (1957) Spastic amaurotic axonal idiocy. A familial juvenile form of a lipo-glyco-protidic thesaurismosis including a pallidal siderosis. In: *Cerebral Lipidosis.* Edited by J. N. Cumings, Oxford: Blackwell, pp. 34-47.

RADERMECKER, J. and MARTIN, J. J. (1972) Dystrophie neuroaxonale et maladie de Hallervorden-Spatz infantiles: Aspects électrocliniques et anatomopathologiques, diagnostic différentiel. *Bulletin de l'Academie Royale de Médecine de Belgique,* **12,** 459-501.

RICHTER, E. (1972) Ein Beitrag zur infantilen neuroaxonalen Dystrophie. Vergleicht der histopathologischen Befunde und des klinischen Bildes mit der Hallervorden-Spatzschen Krankheit. *Zeitschrift für Neurologie,* **201,** 160-195.

RIZZUTO, N., VIO, M., GHERSINI, L. and PANIZON, F. (1973) Seitelberger's infantile neuroaxonal dystrophy. A case report. *European Neurology,* **9,** 321-332.

—— DALLA BARBA, G., BONAN, R., REBESCHINI, V. and AMADUCCI, L. (1969) La dystrophie neuroaxonale infantile de Seitelberger. Étude anatomoclinique d'une fratrie. *Acta Neurologica, Belgica,* **69,** 381-404.

ROZDILSKY, B., BOLTON, C. F. and TAKEDA, M. (1971) Neuroaxonal dystrophy. A case of delayed onset and protracted course. *Acta Neuropathologica, Berlin,* **17,** 331-340.

SACKS, O. W., AGUILAR, M. J. and BROWN, W. J. (1966) Hallervorden-Spatz disease. Its pathogenesis and place among axonal dystrophies. *Acta Neuropathologica, Berlin,* **6,** 164-174.

SANDBANK, U. (1965) Infantile neuroaxonal dystrophy. *Archives of Neurology, Chicago,* **12,** 155-159.

—— LERMAN, P. and GEIFMAN, M. (1970) Infantile neuroaxonal dystrophy. Cortical axonic and presynaptic changes. *Acta Neuropathologica, Berlin,* **16,** 342-352.

SCHEFFNER, D., FEIST, D., KOLKMANN, F. W. and WILLE, L. (1973) Infantile neuroaxonal dystrophy (INAD) diagnosed *intravitam.* Clinical course over years, neuropathological and biochemical findings. In: *Meeting Report of the European Study Group on Child Neurology, Kungälv, Sweden, Sept. 1973.* Läkemedle, Mölnal, Sweden: Geigy.

SCHEITHAUER, B. W., FORNO, L. S., DORFMAN, L. J. and KANE, C. A. (1978) Neuroaxonal dystrophy (Seitelberger's disease) with late onset, protracted course and myoclonic epilepsy. *Journal of the Neurological Sciences,* **36,** 247-258.

SCHNECK, S. (1966) Neuropathological features of human organ transplantation. II. Central pontine myelinosis and neuroaxonal dystrophy. *Journal of Neuropathology and Experimental Neurology,* **25,** 18-39.

SEITELBERGER, F. (1952) Eine umbekannte Form von infantiler lipoid speicher Krankheit des Gehirns. In: *Proceedings of the First International Congress of Neuropathology, Rome.* Torino: Rosenberg and Sellier, 1956, vol. III, pp. 323-333.

SEITELBERGER, F. (1953) Une affection spéciale du métabolisme des cellules ganglionnaires du système nerveux. Lipoïdose infantile tardive atypique du type tronco-cerebello-spinal. In: *Proceedings of the Fifth International Congress of Neurology, Lisboa.* Lisboa: Comptes-Rendus, 1954, vol. II, pp. 92-93.

—— (1971) Neuropathological conditions related to neuroaxonal dystrophy. *Acta Neuropathologica, Berlin,* Supplement 5, 17-29.

—— and GROSS, H. (1957) Über eine spätinfantile Form der Hallervorden-Spatzschen Krankheit. II. Histochemische Befunde; Erörterung der Nosologie. *Deutsche Zeitschrift für Nervenheilkunde,* **176,** 104-125.

—— GOOTZ, E. and GROSS, H. (1963) Beitrag zur spätinfantilen Hallervorden-Spatzschen Krankheit. *Acta Neuropathologica, Berlin,* **3,** 16-28.

SENGEL, A. and STOEBNER, P. (1972) Intérêt de la biopsie neuromusculaire dans le diagnostic de la dystrophie neuro-axonale infantile. Étude ultrastructurale de 3 cas dont 2 familiaux. *Acta Neuropathologica, Berlin,* **21,** 109-116.

SHIMONO, M., OHTA, M., ASADA, M. and KUROIWA, Y. (1976) Infantile neuroaxonal dystrophy. Ultrastructural study of peripheral nerve. *Acta Neuropathologica, Berlin,* **36,** 71-79.

SUNG, J. H. (1954) Neuroaxonal dystrophy in mucoviscidosis. *Journal of Neuropathology and Experimental Neurology,* **23,** 567-582.

—— and STADLAN, E. (1966) Neuroaxonal dystrophy in congenital biliary atresia. *Journal of Neuropathology and Experimental Neurology,* **25,** 341-361.

TAKEI, Y. (1965) Infantile neuroaxonal dystrophy (Seitelberger's disease). *Acta Neuropathologica, Berlin,* **5,** 1-15.

THIBAULT, J. (1972) Neuroaxonal dystrophy. A case of non-pigmented type and protracted course. *Acta Neuropathjologica, Berlin,* **21,** 232-238.

TOGA, M., BÉRARD-BADIER, M. and GAMBARELLI-DUBOIS, D. (1970) La dystrophie neuro-axonale infantile ou maladie de Seitelberger. Étude clinique, histologique et ultrastructurale de deux observations. *Acta Neuropathologica, Berlin,* **15,** 327-350.

—— BÉRARD-BADIER, M., GAMBARELLI, D., PINSARD, N. and HASSOUN, J. (1971) Un cas de dystrophie neuro-axonale ou maladie de Seitelberger. III. Étude ultrastructurale du muscle strié. *Acta Neuropathologica, Berlin,* **18,** 327-341.

TORACK, R. M. and HUGHES, C. (1972) Neuroaxonal dystrophy in subacute dementia. Case report. *Acta Neuropathologica, Berlin,* **22,** 264-268.

WIGBOLDUS, J. M. and BRUYN, G. W. (1968) Hallervorden-Spatz disease. In: *Handbook of Clinical Neurology.* Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, vol. 6, pp. 604-631.

YAGISHITA, S. and KIMURA, S. (1974) Infantile neuroaxonal dystrophy (Seitelberger's disease). Histological and electron microscopical study of two cases. *Acta Neuropathologica, Berlin,* **29,** 115-126.

—— —— (1975) Infantile neuroaxonal dystrophy (Seitelberger's disease). A light and ultrastructural study. *Acta Neuropathòlogica, Berlin,* **31,** 191-200.

—— ITOH, Y., NAKANO, T., OIZUMI, J., OKUYAMA, Y. and AOKI, K. (1978) Infantile neuroaxonal dystrophy. Schwann cell inclusions in the peripheral nerve. *Acta Neuropathologica, Berlin,* **41,** 257-259.

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MEMORY DISORDER IN KORSAKOFF'S PSYCHOSIS

A NEUROPATHOLOGICAL AND NEUROPSYCHOLOGICAL INVESTIGATION OF TWO CASES

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INTRODUCTION

THE most striking feature of Korsakoff's psychosis is a severe and often persistent memory impairment. The patient apparently cannot retain new experiences beyond a few minutes, and there is also a retrograde amnesia which may extend back to events that occurred many years prior to the onset of the illness. There have long been attempts to identify the essential cerebral changes associated with the amnesic syndrome, and the question is also of considerable current interest given the increasing sophistication of both experimental and theoretical analyses of normal human memory function, and of the amnesic syndrome itself. But despite a history of studies going back almost one hundred years, Brierley comments in a recent review (1977) that 'a particular pathological description can be correlated only exceptionally with an amnesia that has been defined with precision. The report of Adams, Collins and Victor (1962) is the only one that has gone some way towards providing this correlation, but even in this study the length of retrograde amnesia and the severity of the disorder of memory for recent events cannot be set beside the neuropathological findings in any one case. Until this has been done for a wide range of retrograde and anterograde amnesia, it will not be possible to define the minimal lesion responsible for either or both'. Referring to his own extensive studies in collaboration with Collins and Victor, Adams (1969) comments that 'unfortunately not a single human example . . . has been adequately studied by clinical and anatomical methods. Our own cases of Wernicke-Korsakoff's disease that were subjected to full anatomical study had not been seen by us nor subjected to proper psychological tests; and those with full clinical studies had not come to autopsy . . . Thus one can see the need for a collaborative effort between clinicians and neuropathologists if our knowledge of the precise anatomy of the memory and learning process is to be consolidated'.

The purpose of the present paper is to report the neuropathological findings in the brains of two cases of Wernicke-Korsakoff syndrome whose memory functions had been studied intensively and quantitatively over a number of years.

Gudden (1896) appears to have been the first (Brierley, 1977) who drew attention to alterations in the mammillary bodies in alcoholic patients, and related his observations to the earlier ones of Wernicke (1881) who reported pathological changes in the walls of the third ventricle and in the grey matter around the cerebral aqueduct and in the floor of the fourth ventricle; Gudden was also the first to relate the pathology described by Wernicke and the functional syndrome described by Korsakoff, and the unity of Wernicke's and Korsakoff's syndromes is now generally accepted (Malamud and Skillicorn, 1956; Delay, Brion and Elissalde, 1958*b*; Victor, Adams and Collins, 1971). Following Victor *et al.* (1971) we shall refer to Wernicke's disease as consisting of the early and more readily reversible and independent neurological symptoms, namely ophthalmoplegia, ataxia, transient confusion-apathetic state, and to Korsakoff's psychosis as consisting of the more enduring amnesic syndrome, which may not be uncovered until after the waning of the confused state, plus more variable features such as confabulation, apathy and loss of insight. While the syndrome is perhaps most commonly seen in alcoholics it is not confined to them, as Korsakoff was aware (Campbell and Biggart, 1939).

While there is a consistent finding running through the large number of neuropathological reports of the brains of Korsakoff patients of changes in the mammillary bodies, there is considerable variation of pathology seen also in the thalamus, the mesencephalon, pons, and cerebellum, with a strong tendency for lesions to lie in a medial position and in particular to lie close to the third and fourth ventricles and aqueduct. Typically cerebral neocortex and hippocampus are spared. Some of these sites of pathological change can be correlated with the symptoms of ophthalmoplegia and ataxia of Wernicke's disease as such, and some may be incidental to ageing and other associated states. There have been some reports of damage restricted to mammillary bodies (see Kant, 1932; Remy, 1942; Delay and Brion, 1954; Gruner, 1956; *cf.* Brierley, 1977, for review). On the other hand, Victor *et al.* (1971), while finding changes in the mammillary bodies in all 53 cases of Wernicke's disease and/or Korsakoff's psychosis they examined, argue nevertheless that lesions in the medial dorsal nucleus of the thalamus are more closely correlated with the amnesic syndrome *per se* than are lesions in the mammillary bodies. The evidence on which their argument is based is, first, that of the 43 cases in which the medial dorsal nucleus was available for study, there were only 5 cases in which this nucleus was spared and these were the only 5 cases in which they could be certain that no memory defect was present during life. Secondly, in the same 5 cases lesions were found in the mammillary bodies. Therefore, the question of whether or not there is a particular critical minimal lesion underlying the amnesic syndrome is still open.

As noted above, precise assessment was lacking of the amnesic features of those cases whose brains were subsequently examined, and therefore it is not clear how much of the variability in neuropathological findings is associated with variations in the degree or quality of the psychological state. In recent years there has been a concerted development of techniques for assessing various aspects of memory dysfunction, leading in fact to suggested re-formulations of the amnesic syndrome itself (Baddeley, 1975; Warrington and Weiskrantz, 1973; Weiskrantz and Warrington, 1975). For example, whilst Korsakoff patients characteristically are poor on tests of recognition and free recall, they can show remarkably good retention when tested with techniques of 'cued recall'. Moreover, a method has now been introduced for assessing the degree of retrograde amnesia (Sanders and Warrington, 1971) and there is a greater variety of methods for studying different aspects of anterograde amnesia, including a 'memory battery' which has been standardized on a normal population and which provides an amnesic profile (Warrington, in preparation). Therefore one may now be in a better position to draw conclusions as to which characteristics of the amnesic syndrome correlate with neuropathological findings and to define the particular syndrome for which a minimal lesion might be critical.

The two cases reported here were assessed for intelligence, short-term memory, retrograde amnesia, anterograde recognition, cued recall, and for interference-effects in verbal memory. Each of these types of assessment involved a minimum of two methods or types of stimulus material. One case was studied over a period of nine years, the other over three years, so that longitudinal aspects of the defect, which turned out to be important in one of the cases, could also be set beside the pathological findings.

CASE HISTORIES

E.A. (born 31.02.07), a bricklayer, was transferred on August 2, 1962 to the National Hospital from the North Middlesex Hospital, where diabetes had been diagnosed, for investigation of memory loss, numbness in the limbs and vertigo. His family reported a five- to seven-year history of inadequate diet and excessive drinking, and that about two months prior to his transfer to the National Hospital he had a sudden onset of confusion and memory loss.

On admission he was disorientated in time and in place and had a very severe memory impairment for past and ongoing events. He failed to learn the topography of the hospital ward and he did not learn to recognize the medical or nursing staff. He appeared to be aware of his memory deficit and at no time when he was under observation was there any clear suggestion of confabulation. On questioning he appeared to have very little knowledge, if any, of events that had occurred during World War II. His behaviour on the ward was somewhat truculent and unco-operative; it was noted in the history obtained from his family that this personality trait was of long standing.

On examination there was horizontal nystagmus to the left and there was defective abduction of the left eye, giving him an uncrossed diplopia. There was bilateral weakness of hip flexion and minimal impairment of co-ordination in the lower extremities, with absent deep tendon reflexes and flexor plantar responses. Sensation was impaired in a glove-and-stocking fashion on arms and legs, and there was also consistent impairment of superficial sensation, to a less severe degree, below the mid-thoracic region.

His general nutrition appeared good; his liver and spleen were not palpable. On investigation a full blood count was normal although the ESR was slightly elevated at 27 mm/h. Serum electrolytes and urea were normal. A glucose tolerance test was mildly abnormal but a pyruvate tolerance curve was within normal limits. The CSF contained one lymphocyte and 70 mg per cent protein. Skull and chest x-rays were normal. An EEG yielded a low voltage record with no diagnostic features. EMG studies of conduction velocities in the right lateral popliteal nerve gave a value slightly below the lower limit of normal, which was considered to be consistent with his polyneuritis. Neuro-otological investigation revealed a 40 dB hearing loss in the 4000 to 8000 Hz range in the right ear and an 80 dB loss in the 2000 to 8000 Hz range in the left ear. He was discharged to his home four weeks later. He was readmitted to the National Hospital in 1967, 1969, 1971, 1974 and 1975 at the request of his family and for detailed investigation of his amnesic state.

His neurological and psychological status remained essentially unchanged until his admission of April 29, 1974. His severe memory deficit for ongoing events remained unchanged, as did his somewhat truculent personality. No further neurological investigations were carried out but some degree of intellectual deterioration was apparent.

During his last admission in 1975, when his psychological status had deteriorated still further, there was evidence on EMI scan of slight dilation of the third ventricle and lateral ventricles. The Sylvian and interhemispheric fissures and many cortical sulci were moderately widened. These findings were considered to indicate a moderate degree of cerebral atrophy. In May 1976 he was admitted to Barnet General Hospital with bronchopneumonia and he died three days later from congestive cardiac failure.

H.J. (born 18.01.24) was a merchant seaman during the last war who subsequently became a meat porter. He was first admitted to the National Hospital for investigation of headaches on March 25, 1974. He was known to have a long (indeterminate duration) history of high alcohol (including methyl alcohol) intake which led to his requiring treatment for general debilitation and gastric complications. On September 13, 1973 when he was an inpatient at the West Middlesex Hospital receiving treatment for a gastric ulcer, he had an acute episode of delirium tremens and was transferred to St. Bernard's Hospital. At that time he was noted to be grossly ataxic and disorientated in time and place. His condition improved with vitamin therapy and tranquillizers, but he absconded and was returned to St. Bernard's Hospital on several occasions. On February 11, 1974 he was noted to have nystagmus and an ataxic gait.

On admission to the National Hospital on March 25, 1974 he was clearly disorientated in time and place and had a very severe memory impairment for both past and ongoing events. He failed to learn his way around the ward and on neither his first nor subsequent admission did he learn to recognize staff or other patients. He was fully aware of his memory deficit, frequently referring to his failure to recall events from all periods of his life. Confabulation was never observed on either admission. On questioning he said he remembered his experiences as a merchant seaman during World War II, but on closer questioning it was clear that his memory for events during that period was quite inaccurate and patchy. He was chronically somewhat depressed and lethargic.

On examination, there was normal acuity, a moderate defect of convergence and bilateral primary vestibular nystagmus on lateral gaze and vertical nystagmus. There was slight limitation of upward gaze and right lateral gaze. There was a bilateral slight ptosis, left more marked than right. There was a brisk jaw jerk. There was some slight weakness of the intrinsic muscles in the hands and some slight wasting of the interossei. Vibration sense was lost below the anterior iliac spine but otherwise sensation was preserved. There was slight ataxia for rapid alternating movements and there was a marked defect of postural ataxia of the cerebellar type on heel/toe walking. The plantars were extensor bilaterally. There were early Dupuytren's contractures bilaterally. There were a few small spider nævi.

Other investigations were essentially normal. Full blood count, sedimentation rate, urea, electrolytes, WR, urine chemistry, liver function tests, serum proteins and electrophoresis, alkaline phosphate, and B12 were all normal. Chest and skull x-rays were normal, a gamma scan was negative, electromyography showed no convincing evidence of a peripheral neuropathy. His EEG was essentially normal but alpha rhythm was slow (8 Hz). Serum folic acid was reduced at 3.0 mg/ml but the red cell folate was within the normal range. A fasting blood sugar was elevated at 196 mg/100 ml and urine sugar was positive.

A diagnosis of Wernicke-Korsakoff syndrome due to alcoholism was accepted and he was transferred to St. Bernard's Hospital on April 5, 1974. He was readmitted to the National Hospital on April 22, 1976 for further detailed psychological investigations of his amnesic state. His medical status and personality were essentially unchanged on this admission and the neurological signs noted in 1974 were still present. No further neurological investigations were carried out at this admission.

During this admission he had several attacks of severe epigastric pain and sweating about 45 min after eating, accompanied by nausea and vomiting. On September 7, 1976 he died shortly after one of these attacks. The cause of death could not be firmly established.

PSYCHOLOGICAL INVESTIGATIONS

Intelligence Test Results

E.A. and H.J. were tested on a shortened version of the WAIS (Similarities, Arithmetic, Digit Span, Vocabulary, Picture Completion, Block Designs, Picture Arrangement) at the time of their first admission. This test was repeated at approximately two-yearly intervals (on four occasions for E.A. and once for H.J.). In addition the Progressive Matrices test was administered to provide a distractor task in a retention experiment. The test results are given in Table 1. H.J. consistently scored within the average range and there was no indication that his level of functioning was below his optimum level, nor was there any evidence of deterioration in his intellectual level during the two-year period he was studied. His Nelson and O'Connell (1978) Reading IQ gave an estimated premorbid IQ of 109. Initially E.A. was able to score at the high average level on the verbal scale of the WAIS and at the average level on the performance scale. This level of performance remained fairly static until 1974 at which time evidence of intellectual deterioration was apparent.

TABLE 1. INTELLIGENCE TEST RESULTS

	V. IQ	*P. IQ*	*Matrices*	*Digits forward*
E.A. (05.05.67)	110	102	—	8
E.A. (24.01.69)	107	101	104	7
E.A. (29.12.71)	101	100	(98)	7
E.A. (29.04.74)	103	88	—	7
E.A. (14.08.75)	94	88	—	7
H.J. (26.03.74)	107	105	103	7
H.J. (26.04.76)	105	103	—	7

IQ and digit spans of E.A. and H.J., tested on various indicated dates. V. IQ = Verbal IQ. P. IQ = Performance IQ. Matrices: Raven's Matrices score. Score in parentheses is from an occasion when test was used as a distractor task in a memory experiment.

Short-term Memory

(1) Forward digit span. The digit span subtest of the WAIS was administered twice to H.J. and on five occasions to E.A. H.J. had a forward span of seven items on both occasions, E.A. had a forward span of eight items when first tested in 1967. On all subsequent occasions he attained a forward span of seven items (*see* Table 1). This level of performance is average.

(2) Short-term forgetting. The Brown-Petersen paradigm was used to assess short-term forgetting. E.A. was a subject in the Baddeley and Warrington (1970) experiment assessing recall of three three-letter words after filled intervals of 0, 5, 10, 30 and 60 s. His recall scores together with the mean performance of the control subjects in that experiment are shown in fig. 1. A somewhat modified procedure was used to test H.J. The test stimuli were triplets of consonants printed on flash cards and presented for 3 s each. Serial addition of a series of random numbers or adding 1 to a series of random numbers were used as the intervening tasks in the delay periods. The recall scores of H.J. and a control group of four subjects (patients with extracerebral lesions) after intervals of 0, 5, 10, 30 and 60 s for each intervening task are shown in fig. 2. For each condition the number of arithmetical computations completed in the delay period was recorded and these are also shown in the figure. Both E.A. and H.J. were able to do these short-term forgetting tasks as well as or somewhat better than the control groups.

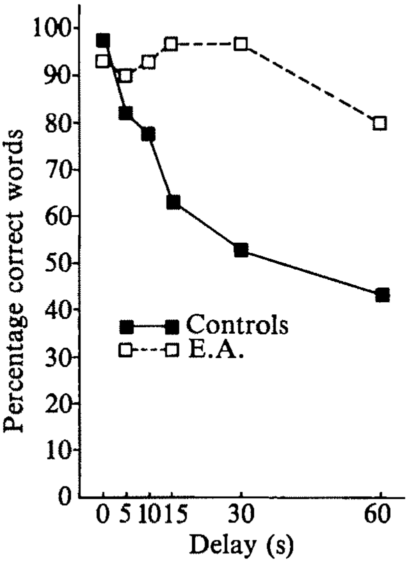


FIG. 1. Recall scores of E.A. and Control subjects for three three-letter words as a function of delay, using Brown-Petersen paradigm. Data from Baddeley and Warrington (1970).

Retrograde Amnesia

A questionnaire about past public events and a memory test of well-known faces were devised to provide quantitative measures of recent and remote memories (for full details *see* Sanders and Warrington, 1971). E.A. was a subject in the Sanders and Warrington (1971) study; his recall and recognition scores on the 'public event'

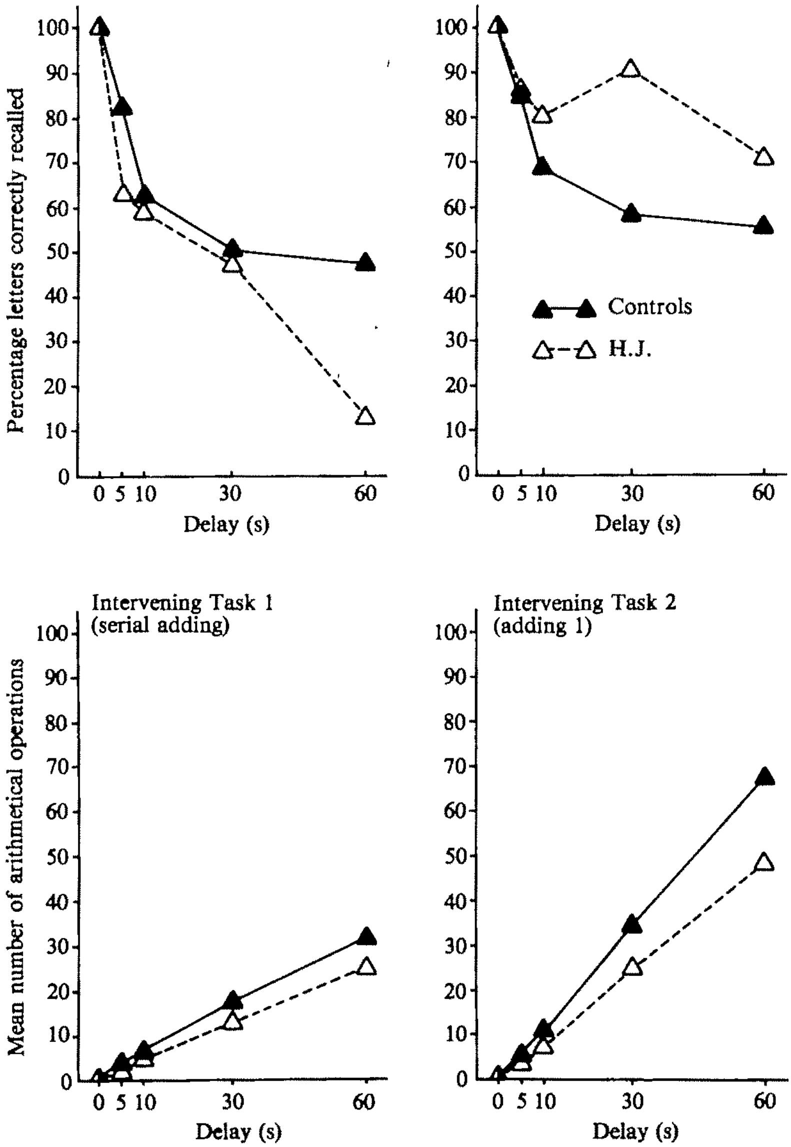


FIG. 2. Recall scores for patient H.J. and Control subjects for consonant triplets, using Brown-Petersen paradigm. Left-hand panels are for condition in which the intervening task was serial addition, right-hand panel for condition in which it was addition of 1 to a random sequence of numbers. Top panels: recall scores. Bottom panels: number of intervening items completed as a function of delay.

TABLE 2. PUBLIC EVENT LONG-TERM MEMORY QUESTIONNAIRE

	1968	*1965*	*1960*	*1955*	*1950*	*1945*	*1940*	*1935*	*1930*
Recall									
E.A.	1	0	0	1	1	1	0	2	1
Controls	7.7	7.1	3.8	4.8	5.0	5.2	6.2	4.5	2.6
Recognition									
E.A.	4	6	6	3	6	5	3	6	6
Controls	10.4	9.8	8.0	7.9	8.1	8.7	9.0	7.4	6.5

Results for E.A. on the Sanders and Warrington (1971) long-term memory test for past public events, according to the time at which the events were topical.

questionnaire, together with those of the Control Group, are given in Table 2. Both E.A. (in 1970) and H.J. (in 1976) were tested on the 'memory for faces' test; their recall and recognition scores are shown in fig. 3. The duration of the retrograde amnesia in each case was extensive, extending over the whole time span sampled in this study (thirty years for E.A. and twenty-five years for H.J.). Memory for remote events was not spared nor did it appear to be less impaired than that for recent events. The possibility that a 'floor' effect masked a differential effect of the age of the event cannot be ruled out, but nevertheless for both patients the retrograde deficit was of relatively long duration.

Anterograde Amnesia

A memory battery based on six subtests has been constructed to encompass different methods of testing retention in the visual and verbal modalities (further details of the test procedures and rationale for their inclusion in the battery are provided by Warrington and Weiskrantz, 1968, 1974; Warrington, 1974). The

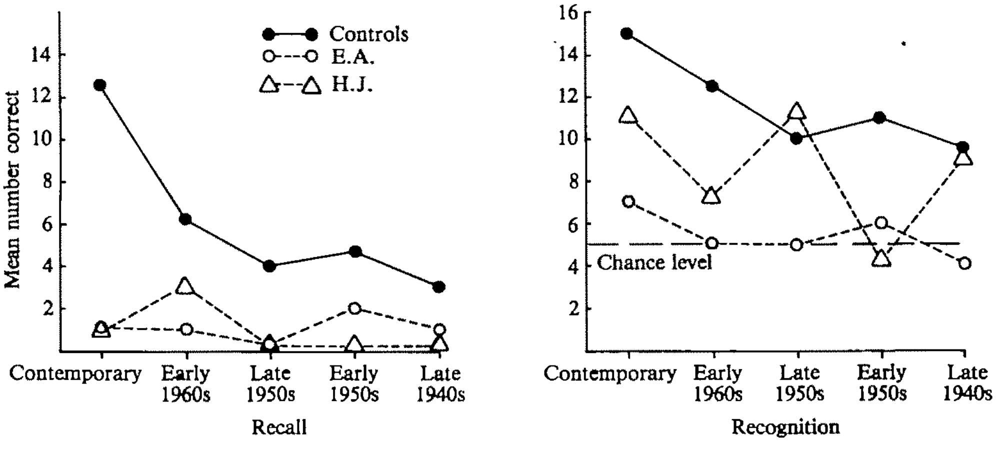


FIG. 3. Memory for well-known faces for E.A. and H.J. and Control subjects, as a function of the period when the faces were topical. Left panel: recall. Right panel: forced-choice recognition.

battery has been standardized on two-hundred normal subjects (Warrington, in preparation). Raw scores are converted to scaled scores, each subtest having a mean scaled score of 10 with a standard deviation of 3. A full-scale memory quotient with a mean of 100 and a standard deviation of 15 can then be computed. E.A.'s and H.J.'s individual scaled scores (corrected for age) for each of six subtests are given in Table 3. (E.A. died before one of the subtests was available in its final form). Both patients' full scale memory quotients were very far off the bottom of the scale, which itself extends to 2.67 standard deviations below the normal mean.

TABLE 3. MEMORY TEST SCORES

Test	*Raw score*		*Scaled score (age corrected)*	
	E.A.	*H.J.*	*E.A.*	*H.J.*
Recognition memory for 50 words (forced-choice, No. correct)	29/50	23/50	0	0
Recognition memory for 50 faces (forced-choice, No. correct)	27/50	27/50	0	0
Verbal retention tested by yes/no recognition (No. correct, No. false positives)	5/32 ($\bar{X} = 25/32$)	1/24	—	0
Verbal retention tested by cued recall (No. correct)	8/32 ($\bar{X} = 11/32$)	16/24	—	11
Learning 10 incomplete drawings (max. 7 trials, No. of errors)	22	24	0	0
Learning 10 incomplete words (max. 7 trials, No. of errors)	6	8	10	8
Memory quotient			< 60	< 60

Test scores for E.A. and H.J. on the memory battery (Warrington, in preparation). Normal scaled scores have a mean of 10 and standard deviation of 3. E.A. died before verbal retention tested by yes/no recognition and by cued recall could be tested using the standardized form of the test, but the mean scores of a Control Group tested with the same material as E.A. are shown in parentheses. Normal memory quotient is 100 with a standard deviation of 15. (*See text.*)

Forced-choice and yes/no recognition memory for both verbal and visual material were markedly impaired in both patients. In contrast, cued recall and incomplete word learning were normal or near normal. However, incomplete picture learning (unlike for normal subjects) was a much harder task than incomplete word learning, and both patients scored off the bottom of the scale. (This result reflects the greater number of errors that the patients made on the task than control subjects over the first seven trials, rather than a failure to learn as such—from previous work we know that amnesic patients can learn such a task, albeit more slowly, and show good retention over long intervals (Warrington and Weiskrantz, 1968).

Interference Effects and Prior Learning

The effect of prior learning and interference phenomena for amnesic retention has been considered in some detail in two previous investigations (Warrington and Weiskrantz, 1974; Warrington and Weiskrantz, 1978). Both E.A. and H.J. were subjects for a 'reversal learning' experiment (Experiment I), the prior learning interference experiment (Experiment II) and the response competition experiment (Experiment III) (for full details *see* Warrington and Weiskrantz, 1978).

(*1*) *Reversal learning*. In this experiment the test stimuli were words with the property that they were the only pairs of words in Basic English that started with the same three letters. The effect of learning one set of words on the subsequent repeated attempts to learn the alternative set is shown in Table 4. E.A.'s and H.J.'s cued recall scores and the control scores are shown separately. H.J.'s and E.A.'s cued recall of list I was as good as that of control subjects, but neither amnesic patient showed any significant learning of the alternative list over four attempts.

TABLE 4. REVERSAL LEARNING

	List 1 *Retention score*	*List 2* *Trial 1*	*List 2* *Trial 2*	*List 2* *Trial 3*	*List 2* *Trial 4*
Controls (mean)	36	24.1	34.5	38.4	40.1
E.A.	33	19	20	25	24
H.J.	37	18	22	21	24

Retention scores for each condition (max. = 45)

Results of 'reversal learning' experiment. Scores are for number of correct words given in response to the cues after prior exposure to the complete words (maximum score = 45). Both patients showed excellent retention of List 1, but poor learning and retention of List 2, using the same cues. (*See text*, and Warrington and Weiskrantz, 1978, Experiment I).

(*2*) *Prior learning and interference*. The test stimuli were word pairs having the first three letters in common so that in each list there was a matched word in the other list (cf. Warrington and Weiskrantz, 1978). Two lists were formed, each consisting of one of the items from each of the pairs. Retention was tested by cueing with the initial three letters. After testing retention of the first list of words, the second list was presented, and then retention was measured for both lists together, i.e. the subject was asked to produce both words that started with the given three letters. The decrement between the initial cued recall score on the first list and the cued recall score on the second list provides a measure of proactive interference and the decrement between the initial first list retention score and the first list retention score after presentation of the second list provides a measure of retroactive interference. These measures for H.J. and E.A. and for the Control Group are given in Table 5. No clear pattern of susceptibility to interference emerges. The overall scores for the two patients were at much the same level as the Control Group, but for H.J. the decrement due to proactive interference was greater and for E.A. the decrement due to retroactive interference was greater.

(*3*) *Response competition*. In an attempt to eliminate interference in memory from incorrect response alternatives, word stimuli were used which could be uniquely specified by their first three initial letters, i.e. no other common English words

TABLE 5. PROACTIVE AND RETROACTIVE INTERFERENCE

	List 1 Initial retention score	*List 1 Subsequent retention score*	*List 2 Retention score*	*% Proactive interference*	*% Retroactive interference*
Controls (mean)	31.3	21.9	24.4	20.8	29.3
	(20–43)	(17–32)	(18–36)	(-10–32)	(15–39)
E.A.	17	14	11	17.6	35.3
H.J.	33	23	17	48.5	30.3

Results of E.A. and H.J. on a test for retroactive and proactive interference. Retention of List 1 words was tested by cued recall, followed by retention of List 1 and List 2 words together. Numbers in parentheses are the ranges of scores of Control Group. (*See text*, and Warrington and Weiskrantz, 1978, Experiment II).

started with the same three initial letters (for example, yacht, onion, juice, etc.). Subjects were first required to generate two-hundred such words given the first three letters of each. The first twenty words which could not be guessed were used as the stimulus words, which were then exposed to the subject. Retention was tested after twenty-four hours by cueing with the initial three letters. The generating and cued recall scores for H.J., E.A. and the Control Group are given in Table 6. The two amnesic patients were superior to the Control Group on both measures (*cf.* Warrington and Weiskrantz, 1978).

TABLE 6. CUED RECALL WITHOUT RESPONSE COMPETITION

	Mean number words generated	*Mean number words recalled*
Controls	125.2	9.5
(mean)	(94–164)	(4–15)
E.A.	164	18
H.J.	156	14

Cued recall (right) of words with response competition minimized, by using words that are uniquely specified by the cues (initial three letters). On left are shown results on preliminary 'generating' phase of experiment. Numbers in parentheses refer to range of Control Group scores. Note that both patients' scores are somewhat better than mean of Control Group. (*See text* and Warrington and Weiskrantz, 1978, Experiment III).

PATHOLOGICAL FINDINGS

E.A.

At post-mortem examination the body was that of a well-developed obese male. The heart showed hypertrophy of the left ventricle and atheromatous changes of the coronary arteries. Slight atheromatous changes were noted in the arteries of the neck and there was marked atheroma of the abdominal aorta. Both lungs showed basal congestion. The gall bladder was fibrosed and contained four mulberry-like stones. The spleen was twice the normal size. The kidneys did not show any significant abnormality. The prostate gland was hypertrophied and nodular.

The brain weighed 1320 g. The leptomeninges did not show any changes to the naked eye. The basal cerebral vessels showed slight atheroma. The sulci of the cerebral cortex were widened. The mammillary bodies were markedly shrunken to about half the normal size (fig. 4). No other abnormalities were noted with naked eye examination.

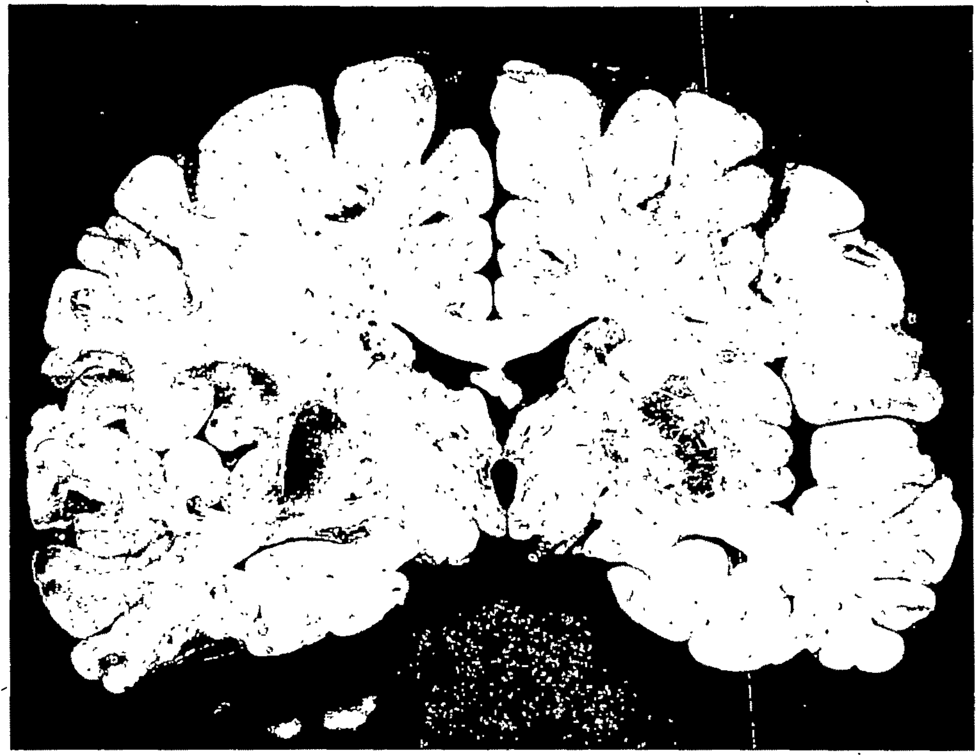
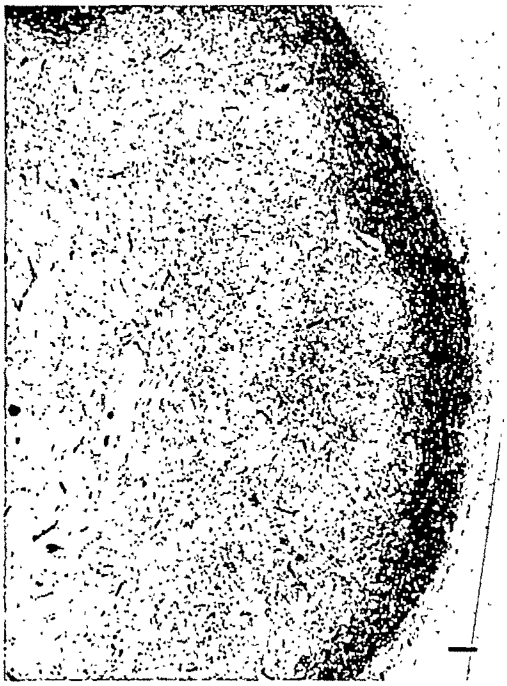


FIG. 4. *E.A.* The mammillary bodies are markedly shrunken.

On histological examination, proliferation of astrocytes with the formation of a dense feltwork of glial fibres was apparent in the medial nuclei of the mammillary bodies in both hemispheres (figs. 5–7). In the left mammillary body cell loss was severe in the dorsal portion of the medial nucleus, having the shape of a wedge with the apex pointing downwards into the ventral portion of the nucleus. In the right mammillary body the cell and fibre loss was somewhat more diffuse and extensive throughout the medial nucleus. The myelin around the mammillary bodies in the bundle of Vicq d'Azyr was preserved.

Throughout the thalamus of both hemispheres there was some increase in the number of astrocytes. However, this increase was particularly intense in a band lying between the medial dorsal nucleus and groups of nerve cells in the subependymal



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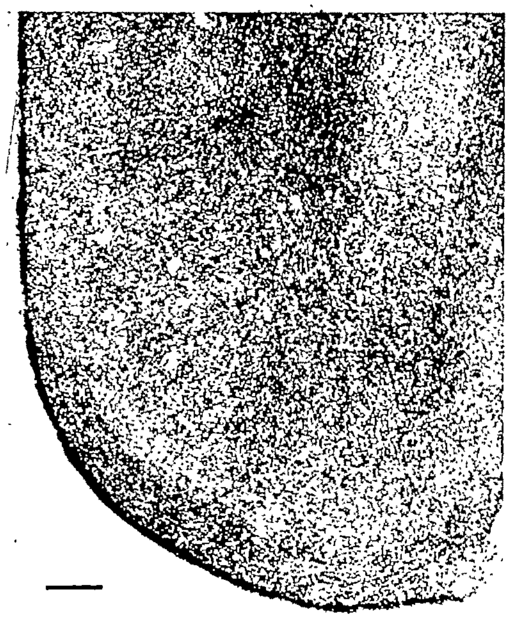

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FIG. 5. *E.A.* Right mammillary body. Myelinated fibres are present around the periphery and the blood vessels are prominent (Loyez, bar = 50 μm).

FIG. 6. *E.A.* Left mammillary body. Marked gliosis is evident throughout (PTAH, bar = 250 μm).

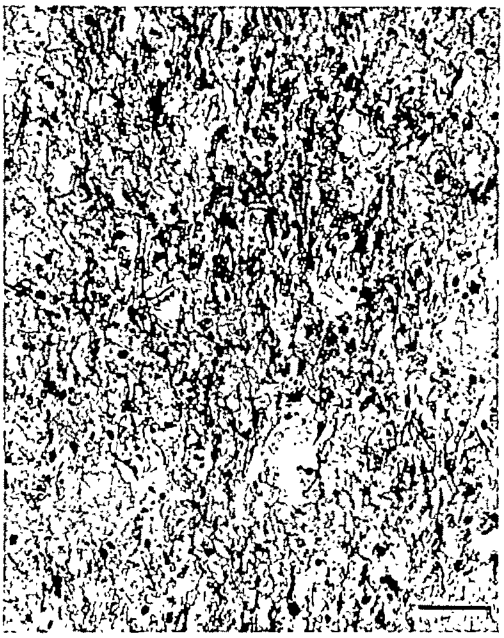

FIG. 7. *E.A.* Left mammillary body. Higher magnification shows severe loss of nerve cells and a dense meshwork of glial fibres (PTAH, bar = 50 μm).

region of the third ventricle (figs. 8, 9). Calcified nerve cells occurred in this band of astrocytes and amongst the nerve cells immediately adjacent to it on either side (fig. 10). More posteriorly in the thalamus the band of astrocytes lay immediately adjacent to the ependyma. The anterior-posterior location of the band of gliosis overlapped with that of the medial dorsal nucleus but also extended anteriorly to it. It lay in the vicinity of the paratenial nucleus and appeared to extend ventrally from that nucleus. Lateral to the band of gliosis the medial dorsal nucleus did not show any obvious loss of nerve cells (fig. 11). Normal magnocellular cells were present. There was no apparent loss of nerve cells elsewhere in any nucleus or region of the thalamus. A small group of macrophages occurred around the white matter related to the pulvinar on the right side, but the pulvinar did not show more astrocyte proliferation than the rest of the thalamic nuclei.

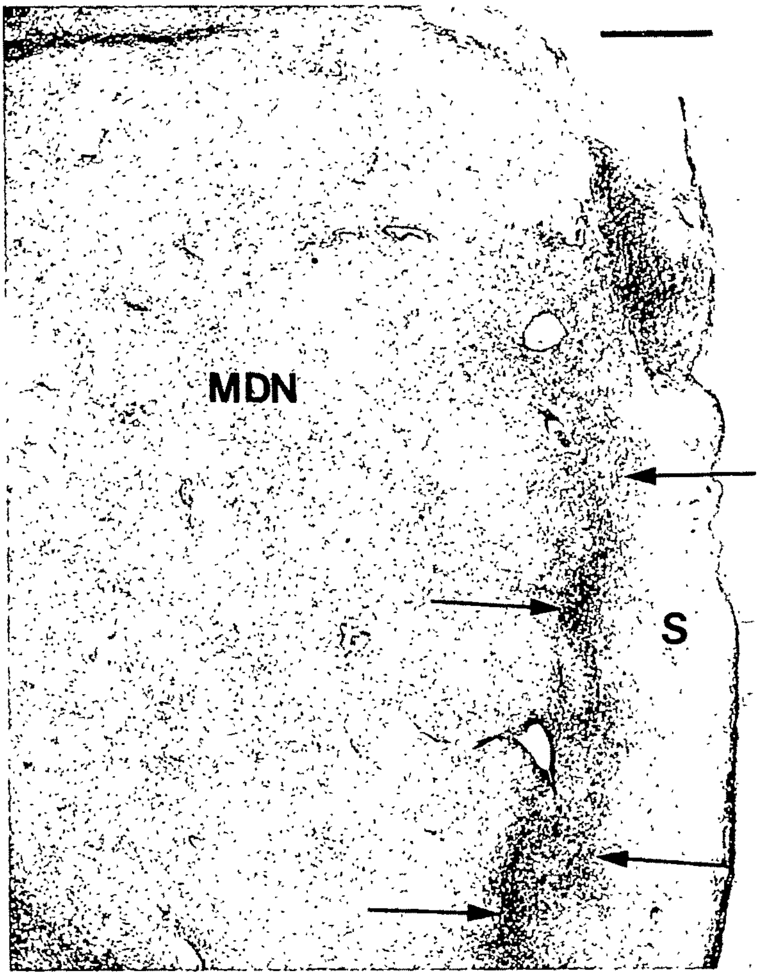

FIG. 8. *E.A.* Left thalamus. A band of gliosis (arrowed) lies between the medial dorsal nucleus (MDN) and the subependymal groups of nerve cells (S) (PTAH, bar = 1 mm).

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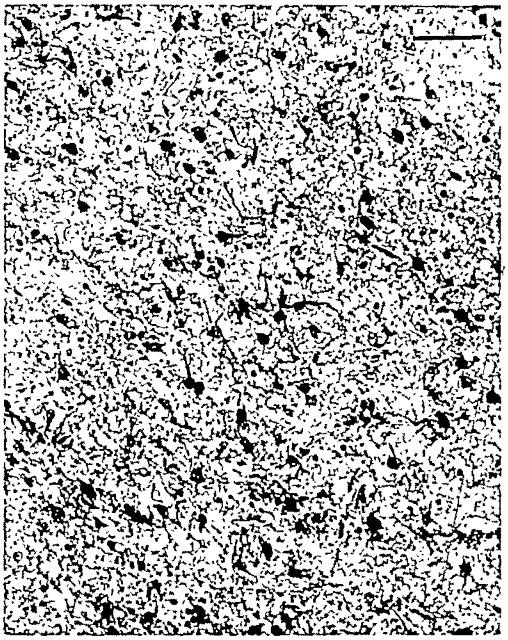

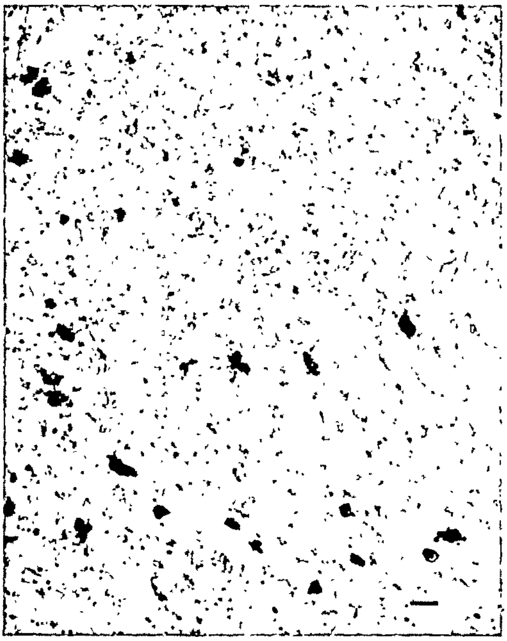

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FIG. 9. *E.A.* Left thalamus. Higher magnification shows an excess of astrocytes and glial fibres (PTAH, bar = 50 μm).

FIG. 10. *E.A.* Left thalamus. Calcified nerve cells are present in the glial band on the medial aspect of the medial dorsal nucleus (HvG, bar = 50 μm).

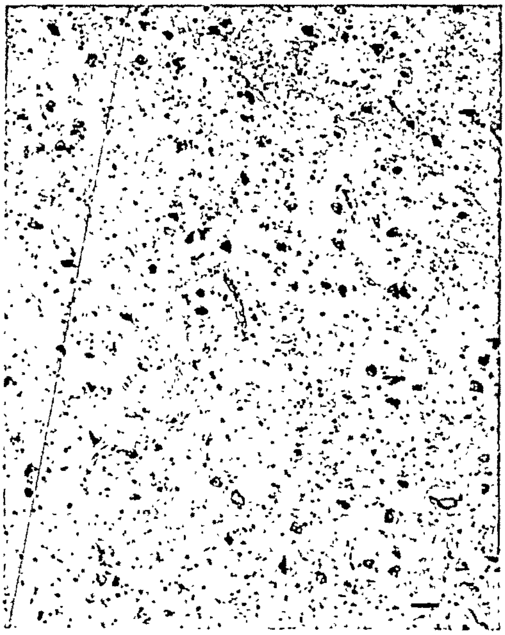

FIG. 11. *E.A.* Left thalamus. No loss of nerve cells is evident in the medial dorsal nucleus adjacent to the band of gliosis (HvG, bar = 50 μm).

There was also some increase in the number of astrocytes in several regions of both hemispheres of the brain. These loci included the parietal and frontal cortex (where there were also very occasional senile plaques and neurofibrillary tangles), the hippocampal and fusiform gyri of the temporal lobe, the hippocampus, caudate nucleus, putamen and globus pallidus, the amygdaloid complex, the subthalamus nucleus, red nuclei, substantia nigra, the vicinity of the aqueduct of Sylvius and the floor of the fourth ventricle and also in the nuclei of the fourth, sixth and seventh cranial nerve nuclei. But in none of these loci was there any evident loss of nerve cells.

In the dorsomedial part of the right cerebellar hemisphere there was a zone of softening showing loss of nerve cells and infiltration by macrophages, and the vessels in the damaged tissue were numerous and congested. Loss of Purkinje cells and proliferation of astrocytes were noted in the folia adjacent to the zone of softening. The left cerebellar hemisphere did not present any lesion. The nerve cells of the dentate nucleus of either side were well preserved but there was a slight increase in the number of astrocytes present.

Further histological examination of the brain was unremarkable. In particular, the fimbria, fornices and corpus callosum were well myelinated, as was the white matter throughout the cerebral hemispheres including the white matter of the temporal lobes and temporal stem. Some macrophages filled with pigment occurred in the white matter near the convexity of the occipital lobe. The optic radiations were well preserved.

H.J.

At post-mortem examination, the body was of a well-developed man who looked his stated years. An old operation scar was present in the abdominal wall. Part of the stomach had been removed and the stomach was anastomosed to the small intestine.

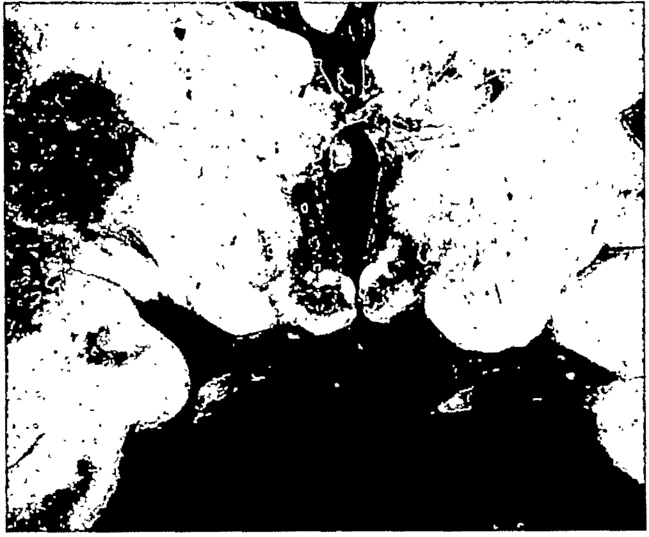

FIG. 12. *H.J.* The mammillary bodies are shrunken and brown in colour.

No lesion was found at the anastomosis nor in the rest of the gut. The lungs were congested and œdematous. No lesions were found in the heart. The liver was congested and the hepatocytes around the central veins of the liver lobules contained a large amount of fat. A mild degree of small round cell infiltration was present in the portal tracts. The spleen was enlarged and congested. A small adenoma was present in the left adrenal gland. No changes of significance were found in the kidneys, urinary bladder, prostate gland, pituitary, pancreas, thyroid and right adrenal glands.

The brain weighed 1510 g. The leptomeninges were not thickened but there was a large amount of clear cerebrospinal fluid and the cerebral sulci were widened and deep. The ventricles were not dilated. The cerebral blood vessels were remarkably free from degenerative changes. The mammillary bodies were markedly shrunken and brown in colour (fig. 12). No other abnormalities were noted on naked eye examination.

On histological examination, the medial nucleus of each mammillary body was congested and the blood vessels were surrounded by numerous macrophages, with the central region of the nucleus showing particularly severe damage. There was obvious destruction of many nerve cells and some proliferation of astrocytes and an increase in the amount of glial fibres (figs. 13, 14). No free iron was demonstrated in

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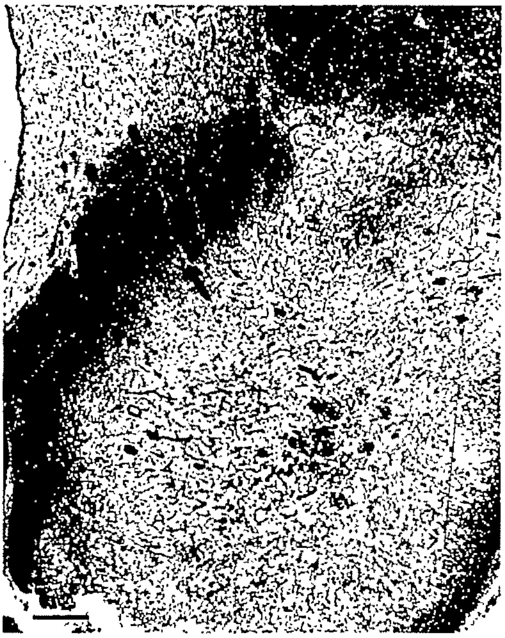

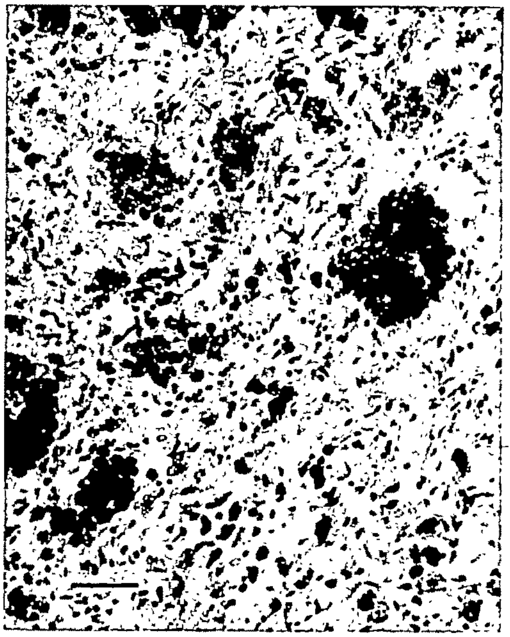

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FIG. 13. *H.J.* Right mammillary body. Myelin is preserved around the body but it presents numerous prominent vessels some of which are surrounded by macrophages (Loyez, bar = 250 μm).

FIG. 14. *H.J.* Right mammillary body, showing collections of macrophages, loss of nerve cells, and proliferation of astrocytes (Nissl, bar = 50 μm).

sections stained with Prussian Blue. The lateral mammillary nuclei were relatively well preserved on both sides.

In each thalamus there was a narrow band of astrocytes between the nerve cells in the subependymal zone and the medial aspect of the medial dorsal nucleus (figs. 15–17). The lesion was somewhat more marked on the left side than on the right, but no calcified cells were noted. At its posterior limit the band of astrocytes lay immediately adjacent to the ependyma. Anteriorly it extended in front of the anterior limit of the medial dorsal nucleus. It lay in the vicinity of the paratenial nucleus and appeared to extend ventrally from it. Lateral to the band of gliosis the

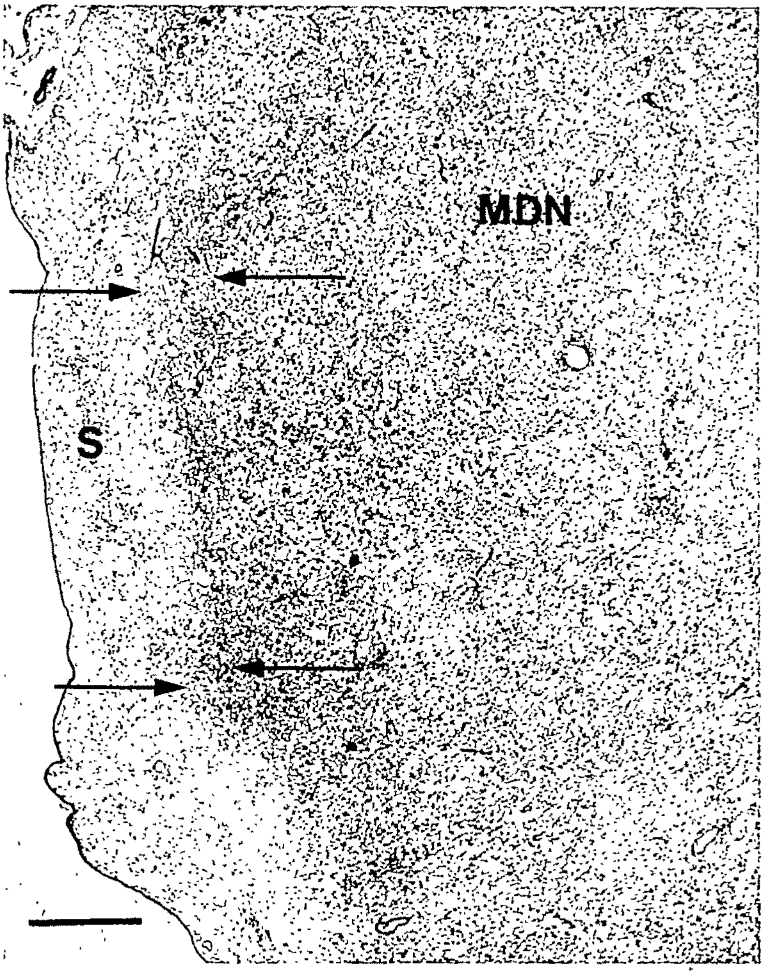

FIG. 15. *H.J.* Right thalamus. A band of gliosis (arrowed) lies between the medial dorsal nucleus (MDN) and the subependymal groups of nerve cells (S) (HvG, bar = 1 mm).

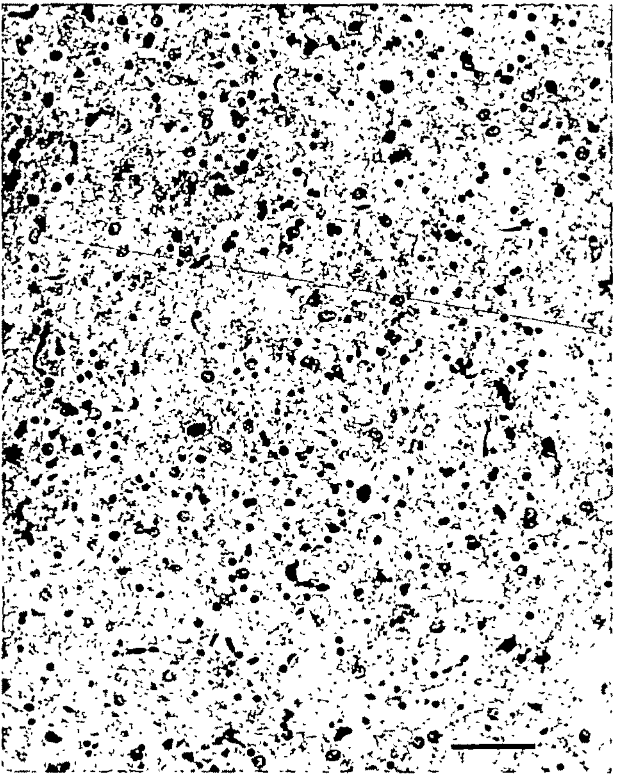

FIG. 16. *H.J.* Right thalamus. Higher magnification shows astrocyte proliferation in this glial band (PTAH, bar = 50 μm).

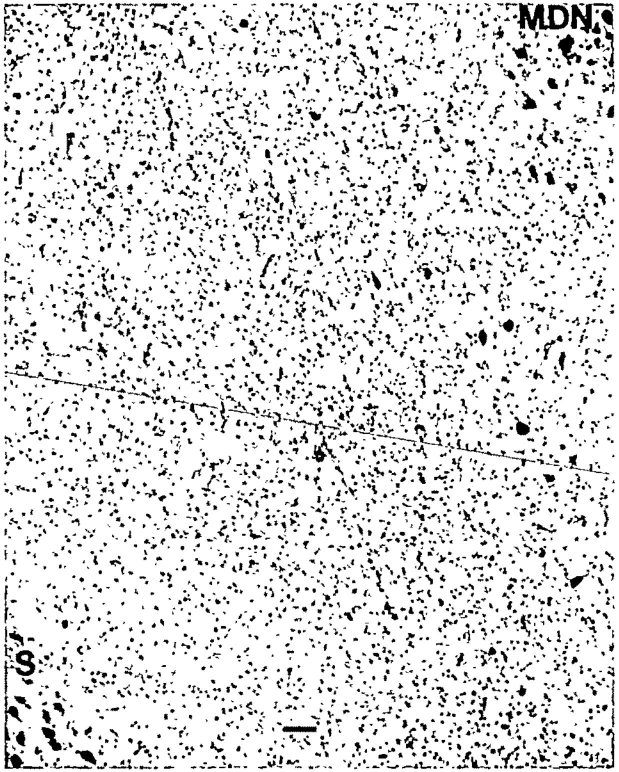

FIG. 17. *H.J.* Right thalamus. The excess of astrocytes is restricted to a band between the medial dorsal nucleus (MDN) and the groups of subependymal nerve cells (S) (HvG, bar = 50 μm).

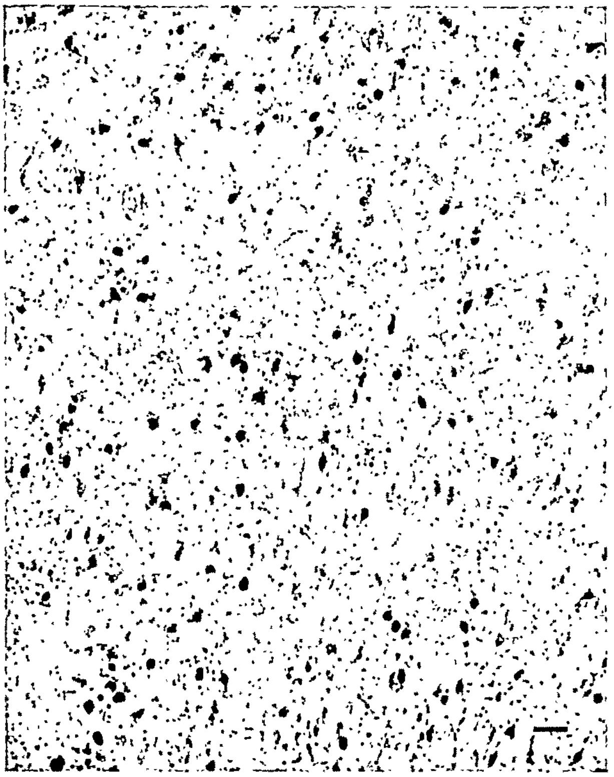

FIG. 18. *H.J.* Right thalamus. The medial dorsal nucleus adjacent to the glial band does not show any evident loss of nerve cells (Nissl, bar = 50 μm).

medial dorsal nucleus appeared normal (fig. 18). Apart from the band of gliosis all other nuclei and regions of the thalamus appeared normal, with no loss of nerve cells or proliferation of astrocytes.

Aside from perhaps a slight increase in the number of astrocytes in the amygdaloid complex on either side and some increase of astrocytes in the dentate nuclei of the cerebellum (but with no loss of nerve cells or increase in glial fibres in any of these structures), all other regions examined appeared normal, including cerebral cortex, thalamus, the structures in the vicinity of the ventricles, the hippocampus (figs. 19, 20) (including the pyramidal cell layer, the dentate fascia and dentate area), the substantia nigra, red nuclei, caudate nucleus, putamen, globus pallidus, midbrain, pons and medulla. Alzeimer's plaques and neurofibrillary tangles were not seen in sections examined from the frontal and temporal lobes. The myelin of the stria terminalis, the fornices and fimbria was well preserved, as was the white matter throughout the cerebral hemispheres including that of the temporal lobe and temporal stem. The myelin overlying the hippocampus was well preserved.

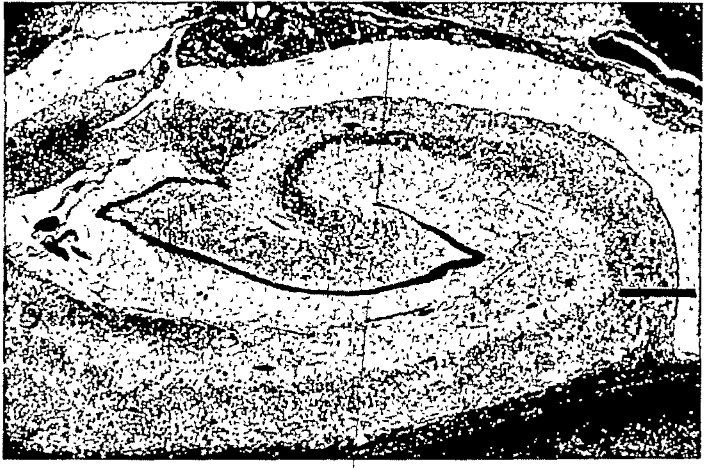

FIG. 19. *H.J.* Left hippocampus. It has an entirely normal appearance (Nissl, bar = 2 mm).

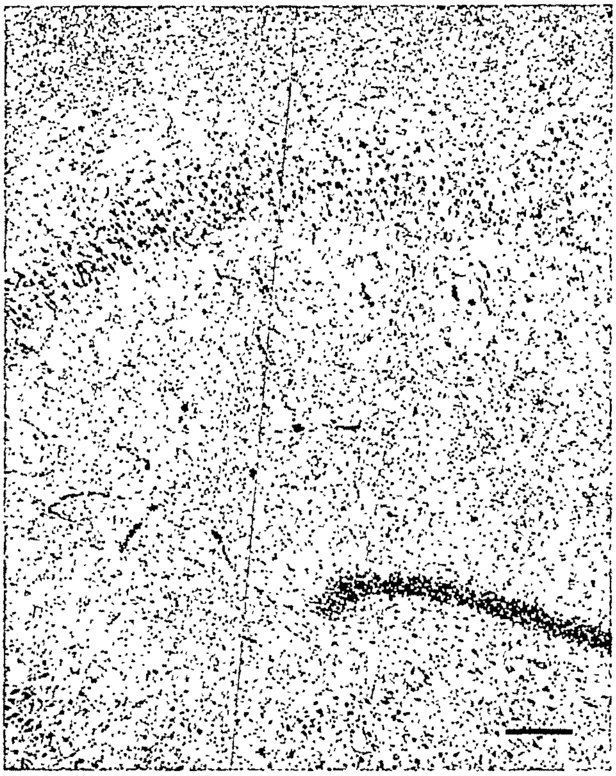

FIG. 20. *H.J.* Left hippocampus. The pyramidal cell layer and the dentate fascia do not show any apparent loss of nerve cells or gliosis (HvG, bar = 250 μm).

DISCUSSION

In the brains of both patients there was marked gliosis, shrinkage, and unusual colouration in the mammillary bodies, in which the pathological changes were much more severe than anywhere else in the cerebral hemispheres. In addition, in both there was a thin band of gliosis bilaterally between the wall of the third ventricle and the medial dorsal nucleus of the thalamus, its rostral limit lying anterior to the medial dorsal nucleus. In patient H.J. these were the only pathological changes that were seen. Patient E.A., in addition to showing a very similar pathological picture in these two bilateral sites, had an increase in astrocytes in various regions of the cerebral hemispheres and the cerebellum, as not uncommonly reported in the literature on Korsakoff's psychosis. H.J.'s severe amnesic state was uncomplicated by any deterioration in intelligence, whereas with E.A. there was clear evidence of a decline in intelligence in the two years prior to his death, although in absolute terms he remained within the low normal range. On this evidence it seems reasonable to correlate the more widespread changes in E.A. with a more general functional loss, and to assign the remarkably restricted memory loss in H.J., as well as the restricted memory loss seen in E.A. at an earlier stage, to the pathological changes in the mammillary bodies and/or the midline thalamic region. E.A.'s absolute intellectual level was such that, had he not been followed closely and repeatedly prior to his death, he might well have been classified as a typical Korsakoff case in which a correlation of his amnesic state could have been emphasized with pathology in one of a number of loci. The importance of longitudinal studies and of estimates of premorbid intellectual capacity for drawing conclusions about clinico-anatomical correlations becomes self-evident.

The minimal lesion for the alcoholic Korsakoff amnesic state, from our evidence, would appear therefore to be in the mammillary bodies or in the midline region of the thalamus, or both. That a combined mammillary body and thalamic lesion is necessary would be consistent with the evidence of Victor *et al.* (1971), although they themselves appear to favour the view that a medial dorsal thalamic lesion itself is a sufficient condition. In the brains of 26 cases diagnosed as having a Korsakoff memory disorder (with or without Wernicke's disease), both the mammillary bodies *and* the medial dorsal nucleus were abnormal in all cases (Table 28, p. 139). A combined lesion is also consistent with a recent report by Mishkin (1978) that amygdala plus hippocampal lesions in the monkey cause a very severe impairment of visual recognition memory, which he considers might mimic the amnesic syndrome associated with medial temporal resections or pathology in man, whereas either lesion alone produced a much less severe deficit. In man, medial temporal surgical lesions (Scoville and Milner, 1957) or pathology associated with encephalitis (Hierons, Janota and Corsellis, 1978) causing an amnesic syndrome which we have argued (Weiskrantz and Warrington, 1975) is similar psychometrically in many essential respects to the Korsakoff amnesic state, involve both the hippocampus and the amygdala, as well as overlying white matter. Hippocampal damage would lead to degeneration in the mammillary bodies consequent upon fornix degeneration (for example, in all the brains of patients with temporal lobe encephalitis and with memory disorders studied by Hierons *et al.* (1978) the mammillary bodies were also pathological). While H.J.'s amygdaloid complexes appeared normal, it is possible that tracts in or out of the amygdala might have been abnormal. Recent evidence (J. P. Aggleton, personal communication) using horseradish peroxidase labelling has demonstrated a projection in the rhesus monkey from midline thalamic nucleus (but *not* the medial dorsal nucleus) to the amygdala. (In the rat (Krettek and Price, 1977) and the monkey (Kievit and Kuypers, 1977) there is a projection from midline nuclei to the orbital frontal cortex). Also it would be difficult to rule out the possibility of abnormal output tracts from the amygdala. The stria terminalis, for example, is only a poorly myelinated tract and although there is no suggestion that it was abnormal in either H.J. or E.A., one would require much finer quantitative analysis and age-related norms to arrive at an absolutely firm negative conclusion.

While we found changes in two separate sites, it remains a logical possibility of course that they had a single cause or that the thalamic degeneration was a secondary consequence of the lesion of the mammillary body. For example, in addition to the well-known fornical connections to the mammillary bodies, a bundle of degenerating fornical fibres is described by Valenstein and Nauta (1959) in the monkey (as a result of a lesion in the fornix plus septum) that follow the stria medullaris and terminate in the medial portion of the medial dorsal nucleus of the thalamus (*see also* Guillery, 1956). In the cat and rabbit some of the fibres originating in the mammillary bodies cross the midline and terminate in the contralateral thalamus (Fry, Krumins, Fry, Thomas, Borbely and Ades, 1963); their course in man, if they exist, is not known, but they might be vulnerable to degeneration with mammillary body pathology. But, as we shall see, pathological changes in the medial thalamus are not an invariable consequence of lesions of the mammillary body in patients with alcoholic Wernicke's disease, although perhaps it is in those cases that suffer from a particular variety of the amnesic syndrome.

On the other hand, a closer comparison of our findings with those of Victor *et al.* (1971) could be taken to support the view that the critical lesion for the amnesic syndrome is restricted to the mammillary bodies, because that is the only site of pathological change common to all their patients with diagnosed memory disorders and to our two patients. Both their patients and ours also showed changes in the thalamus, but apparently in different loci. Victor *et al.* identify the pathological changes in their patients as lying in the medial dorsal nucleus ('when minimally involved, it was affected in its ventro-medial portion; maximally the disease affected the entire medial (*magnocellular portion*) with a series of finger-like projections extending laterally.' p. 90, italics added). Using the same nomenclature source (Kuhlenbeck, 1954) we would place the thin band of gliosis in our patients as lying medial to the medial dorsal nucleus and extending anterior to it, in the vicinity of the paratenial nucleus. In sections posterior to the gliosis, large cells in the medial dorsal nucleus are seen bilaterally and they and the whole of the nucleus appears normal in both our patients. Dr T. P. S. Powell, Department of Human Anatomy, University of Oxford, kindly examined very carefully the sections through the thalamus, as well as many others, and confirmed the description of the loci of pathological changes in the two brains given here. The question of nomenclature, however, is a serious one. Kuhlenbeck (1954, p. 45) refers to the variable and irregular intermingling of the magnocellular and parvocellular elements in the human medial dorsal nucleus and considers that they are not clearly delimited. Van Buren and Borke (1972, Vol. 1, pp. 66–68) also discuss the considerable variability of the magnocellular region of the nucleus and refer to the work of Feremutsch and Simma (1955) in which it was absent in 50 per cent of their material. The nuclear boundaries in the medial thalamus are not sharp. The loci of pathological changes in this region, therefore, are better assessed from illustrations of sections than from verbal labels. On this basis, in the only figure of the medial dorsal nucleus shown by Victor *et al.* (1971, fig. 25) the gliosis would appear to extend further laterally than in our two cases, well into the body of the medial dorsal nucleus, but perhaps overlapping medially. The limit would appear to lie even further laterally in the low-power sections (figs. 5 and 6) shown by Delay and Brion (1969). On the other hand, the gliosis seen in the one section of Malamud and Skillicorn (1956, fig. 4) would appear to lie in the same general zone as in our cases, which is referred to as the dorsal medial nucleus by those authors.

But the conclusion that the critical thalamic locus in our patients is different from that of Victor *et al.* may be premature, aside perhaps from the intrinsic difficulty of defining the exact medial limit of the medial dorsal nucleus. Victor *et al.* do not offer statistics on the incidence of pathological changes in the region of the paratenial nucleus in those cases specifically diagnosed as having a Korsakoff memory disorder, as distinct from the group as a whole that had symptoms either of Wernicke's disease and/or of memory disorder. Where the Korsakoff subgroup is considered separately, the only thalamic nucleus that is listed in the tabular summary of results is the medial dorsal nucleus (Table 28, p. 139). It is possible therefore that all cases of memory disorder in the series of Victor *et al.* had thalamic pathological changes in the same locus as seen by us, as well as in the medial dorsal nucleus and possibly other thalamic sites. In only 8 out of 38 cases was the medial dorsal nucleus said by Victor *et al.* to have been the only thalamic nucleus involved, and as these 8 cases were not considered in relation to the presence or absence of a memory disorder, such a possibility seems not unlikely. On the other hand, they also assert that 'without exception, no nucleus was affected when a nucleus with a higher over-all incidence was unaffected.' (p. 89). Such an assertion would have to be based on a complex, indeed formidable construction of a large matrix of results, as 23 thalamic nuclei appear in their Table, but if the site of medial pathological changes in our study is genuinely different from the medial dorsal site of Victor *et al.*, this would mean that our finding of changes in a low-incidence site (paratenial nucleus—32.4 per cent, Table 21, p. 88) in the absence of any in the high-incidence medial dorsal site (88.4 per cent) would be an important exception to their findings.

The question of the necessity of pathological changes in the thalamus could be settled if there were well attested cases of the Korsakoff amnesic syndrome in the absence of such changes (or in the respective cortical projection areas). There have been a number of such reports (*see* Remy, 1942; Gruner, 1956; Delay and Brion, 1954; Kant, 1932; Malamud and Skillicorn, 1956). In none of these are more than sketchy details of the amnesic state provided. The clinical case history provided by Remy is fuller than usual; it is of an alcoholic Korsakoff patient whose state was reported as being stable over ten years (although there is also a comment that he became increasingly 'confused and disoriented' over that period). The anterograde amnesia appears to have been severe, and there was a retrograde amnesia whose severity it is difficult to judge: he could not remember his internment in hospital when questioned four months after the event, but nothing is said about his memory for events that occurred before this, other than that he could remember his brothers and sisters, his place of birth, and his 'troubled' childhood. Remy emphasizes that there were no signs of neuropathological changes other than a severe lesion of the mammillary bodies, with no changes in the diencephalon, mesencephalon and telencephalon. There is, however, a slightly curious statement, which receives no further amplification, that 'the thalamus was small in comparison with the corpus striatum, which was voluminous'. (p. 137), but it must be presumed that the thalamus appeared normal histologically. The neuropathological report of a case by Delay and Brion is relatively detailed. Apart from a severe bilateral lesion in the mammillary bodies, there were a few small regions of glial proliferation in the subependyma around the third ventricle, in the septum and aqueduct of Sylvius, and 'signs of axonal reaction' in the dorsal raphé nucleus and also some changes in the olives. No other lesions were found anywhere else in the brain. Unfortunately, no details whatever are provided of the psychological background, beyond the statement that the patient was an alcoholic with a 'typical Korsakoff syndrome'. No details are provided either of the memory defect in the 8 Korsakoff patients whose brains were examined by Delay *et al.* (1958*a*), beyond stating that they had both retrograde and anterograde amnesia. The mammillary bodies were pathological in all 8 cases, but the thalamus—including the 'inner' nuclei and the anterior nucleus—were said to be normal. Malamud and Skillicorn (1956) examined the brains of 70 patients, mainly alcoholic Korsakoff cases, all of whom were said to have 'memory impairment' of the Korsakoff type, 94 per cent of whom also had 'disorientation and confusion'. All the brains were abnormal in the periventricular and periaqueductal region, 95.7 per cent had abnormal mammillary bodies, but the medial dorsal nucleus of the thalamus was seen as abnormal in only 52.8 per cent and the pulvinar in only 4.2 per cent (no other thalamic nuclei are listed). The report by Gruner is also rather sketchy, both as regards pathology and psychological state, although he does conclude that 3 out of 4 Korsakoff cases (out of a larger population of 17 alcoholic cases) had pathology relatively *isolated* in the mammillary bodies. A somewhat similar but fuller account is given by Kant of the brains of 17 alcoholics, in which 2 were said to have pathology restricted to the mammillary bodies. A brief account is given by von Örthner (1957) of 2 cases of Korsakoff's psychosis associated with secondary carcinomas restricted almost entirely to the mammillary bodies. Therefore, while the positive evidence cannot be said to be strong there are also no good grounds for rejecting the conclusion of a number of authors that the mammillary bodies can be the only pathological structures in the brains of Korsakoff patients, and that the thalamus need not appear abnormal.

The same question can be asked about the necessity of mammillary body pathology: are there any well attested cases of the amnesic syndrome in the absence of abnormal mammillary bodies (or of structures to which they are directly connected in the hippocampal-fornix-septal system; *cf.* Ciba Foundation Symposium No. 58, 1978)? There are a few scattered relevant reports in the literature. Thus, Riggs and Boles (1944) reported that the mammillary bodies were affected in 21 out of 23 cases of Wernicke's Disease. But the disorders of memory were not described in any detail; indeed, the only relevant features listed were 'mental confusion' and 'clouding of consciousness'. Similarly, Delay, Boudin, Brion and Barbizat (1956) list one case of Korsakoff's psychosis (among 8 alcoholic cases) in which the mammillary bodies were free of pathological changes. But there was diffuse subcortical atrophy in that case, and the clinical and anatomical details are meagre. It is not clear in the report by Malamud and Skillicorn (1956) whether the 3 cases (out of 70) in which there were no mammillary body pathological changes differed from the 67 in which there were. As already noted above, all 70 cases had a 'memory impairment' but no further psychological details are offered. All 70 cases also showed periventricular and periaqueductal pathological changes, which could have directly affected connections to and from the mammillary bodies. Certainly the characteristic finding in the vast majority of cases of Korsakoff's psychosis is of shrunken, discoloured and gliosed mammillary bodies, especially in the medial nucleus, the pathology being visible to the naked eye (useful reviews are provided by Delay, Brion and Elissalde, 1958*b*, and Delay and Brion, 1969) and in this purely statistical sense there can be little doubt of the appropriateness of the stress that Gamper (1928) laid on the implication of these structures in the Korsakoff amnesic state. Additional pathological changes, on the other hand, may sometimes be uncovered only after a more exhaustive microscopic search and, when discovered, may be confined to relatively small foci, as in the two cases reported here, although typically are more widespread in the region of the third and fourth ventricles.

It may be noted that in our two cases the hippocampus as well as the white matter in the 'temporal *stem*' were well preserved and normal in appearance bilaterally and thus do not lend support to the recent speculation that the temporal stem may have a critical role in amnesia (Horel, 1978).

Recently a case has been reviewed by McEntee, Biber, Perl and Benson (1976) of an instance of an apparent amnesic syndrome associated with bilateral tumour invasion of the medial and posterior thalamus, without direct involvement of the mammillary bodies. 'The caudal aspect of the third ventricle was filled with grey-white, granular, friable tissue which was contiguous with a large midline mass invading the medial aspect of the thalamus bilaterally and extending along the Sylvian aqueduct into the dorsal midbrain to the level of the rostral pons. In its greatest extent, the mass measured approximately 3.0 cm mediolaterally by 3.5 cm rostrocaudally.' (p. 438). Indirect effects on the mammillary bodies were discounted as, in this case, they 'were reasonably separated from the tumour mass and were free from œdema when examined by conventional methods.' (p. 439). (Ample evidence exists for an association between third ventricle tumours and Korsakoff type amnesic memory disorders, *see* Williams and Pennybacker, 1954; White and Cobb, 1955, but not excluding either direct or indirect pathological effects on the mammillary bodies). There were, in addition, smaller tumour foci in the septum and the floor of one temporal horn, but not involving Ammon's horn. While considering that their results support the contention of Victor *et al.* (1971) that the medial dorsal nuclei can be associated with amnesia, they also conclude from their review of the tumour literature that 'the thalamus in the region of the dorsal medial nucleus is not consistently involved in patients with tumours occurring in association with amnesia' (p. 440), and suggest that 'small lesions in a number of different sites, the anatomical relationship of which is not yet entirely clear, can produce remarkably similar and profound memory disturbances' (p. 440).

The case of McEntee *et al.* is representative of many clinical reports in which it is difficult to assess the cognitive status of the patient, who in this instance became drowsy and inattentive within a week of admission, and within two weeks lapsed into a deep stupor. It would appear that the patient had a reduced digit span (unlike our two patients), and also probably a significant reduction of IQ, as simple arithmetical subtractions were failed. He was said to have considerable difficulty in manipulating old knowledge. There were conspicuous emotional changes, as well, and there was a report that 'the patient had failed to recognise his son until the son spoke to him'. (p. 438).

These features can be contrasted with Talland's (1965) characterization (*cf.* Adams, 1969) of some cases of Korsakoff's psychosis as showing preservation of normal capacity to think, solve problems, with little if any reduction in intelligence test scores, preservation of an alert wide-awake state of mind, ability to perceive, imagine, speak, and calculate with customary speed and efficiency (all of which were also seen with H.J. and with E.A. until two years prior to his death). Disentangling the amnesic features of Korsakoff's psychosis, the characteristic paucity of speech, from the confusional state of Wernicke's disease and of other acute neurological conditions may be difficult in an uncontrolled clinical situation. Also, the amnesic feature of Korsakoff's psychosis may be far from stable, quite aside from variations in severity even when stable. Thus, Victor *et al.* (1971, pp. 42–43) report that 21 per cent of their clinical population who could be followed (104 cases) showed 'complete' recovery and another 25 per cent showed 'significant' recovery from

Korsakoff's psychosis; of those that recovered completely almost all did so within a period of one to ten months (*see also* Adams, 1969, p. 99).

Thus far we have been considering only instances of alleged amnesia and the locus of subsequently revealed pathological changes. But the support for or against particular critical loci has sometimes been based on negative evidence, that is, on cases who were said *not* to be amnesic but had circumscribed neuropathology. Victor *et al.* base their support for the importance of the medial dorsal nucleus of the thalamus largely on the fact that there were 5 brains (out of 43 in which the medial dorsal nucleus was available for examination) which were free of pathology in this nucleus, and these cases were the only ones *known not* to be amnesic. In these 5 cases the mammillary bodies were abnormal; the lesions were described as being as severe as in the other cases with an amnesic state, and in 3 out of the 5 to be of the chronic type. The 5 patients had suffered from Wernicke's disease but the 'apathetic-confusional state, ocular and taxic signs subsided, leaving them without sensorial defects and *without* Korsakoff's psychosis'. (M. Victor, personal communication). But we cannot be certain of the psychological status of the remaining 38 cases: out of the total population (53 cases, Table 20, p. 83) in which brains became available there were only 26 in which a positive psychological diagnosis of the Korsakoff amnesic syndrome could be confirmed, and therefore it may be that patients other than the 5 were also not amnesic, that is, had pathological changes in the medial dorsal thalamus without amnesia. (Only one-third of the post-mortem cases studied by Victor *et al.* had been carefully observed by them; the diagnoses of the rest were based on recorded clinical observations of others). To demonstrate that pathology of the medial dorsal thalamus is sufficient to produce the amnesic state it would be required to have at least one unambiguous case of Korsakoff's psychosis with pathology of the medial dorsal thalamus in the absence of any such changes in the mammillary bodies, and we are not aware that any such case has been reported. Bilateral stereotactic lesions presumed to be in the medial dorsal nucleus of the thalamus in man (Spiegel, Wycis, Orchinik and Freed, 1955) produced (in some cases) only a transient temporal disorientation, never a stable amnesic syndrome.

There are also other instances of reported mammillary body abnormality in the absence of memory disturbance (Tsiminakis, 1931; Delay *et al.*, 1956; Gruner, 1956). But even careful microscopic examination of the mammillary bodies might be inadequate for arriving at a satisfactory conclusion as to the severity of the functional abnormality. For example, Adams (1969) comments that in patients in the Victor *et al.* series, nerve cells tended to be less affected than medullated fibres, and in the reports by Delay and Brion (1954) and Delay *et al.* (1958) of Korsakoff cases the mammillary bodies were shrunken and showed proliferation of microglia, but loss of neurons was relatively slight, as was also the case in most of the brains in the Malamud and Skillicorn report (1956). Appreciable cell loss was found in both our cases, and also in the case studied by Remy (1942) in which pathological changes were said to be confined to the mammillary bodies, but it is very difficult to compare reports with each other quantitatively. Also, the mechanism of the presumably metabolic ætiology of Korsakoff pathology is not understood, and the severity of the functional disorder may depend on the level of metabolic requirements available to the mammillary body cells, which may in turn depend on a more delicate mechanism than can be assessed from histopathological evidence as such. (It is of possible significance in this connection that the de-oxyglucose labelling technique reveals a high rate of energy utilization in the mammillary bodies of monkey (Kennedy, Sakurada, Shinohara, Jehle and Sokoloff, 1978) and of rat (Sokoloff, Reivich, Kennedy, Des Rosiers, Patkak, Pettigrew, Sakurada and Shinohara, 1977), perhaps rendering them especially sensitive to reduction in metabolic requirements).

A possibility consistent with the evidence is that a lesion in the mammillary bodies, if severe enough, is sufficient by itself to result in the amnesic syndrome, but that less severe damage in that site will be insufficient unless one or more other structures, for example, medially placed nuclei of the thalamus, are also abnormal. We have seen that there have been a number of claims that a lesion in the mammillary bodies can be sufficient to produce a Korsakoff memory disorder, whereas the evidence that a medial thalamic lesion can be sufficient is more problematical. Alternatively there may be a mass action relationship among various thalamic and hypothalamic structures in the vicinity of the third ventricle such that an extensive enough lesion, irrespective of its locus within these structures, will cause the syndrome. But, finally, without precise assessment of the psychometric profile and evidence as to the severity and stability of the memory disorder in various studies, it is impossible to know if one is comparing like with like. There is often a striking imbalance in published reports between the fineness of microscopic detail with which the neuropathology is recorded, and the grossness or even absence of psychological descriptions, to which Brierley repeatedly draws attention in his recent review (1977). It will remain impossible to assess how much of the variation in loci of pathology can be accounted for by variation in the amnesic phenomena themselves until the latter are characterized, classified, and measured on common scales.

Recently a notable report has appeared attempting to relate the severity of amnesia, assessed quantitatively, to the concentration of monoamine metabolites in the cerebral spinal fluid of Korsakoff patients (McEntee and Mair, 1978). There was a negative correlation between severity of amnesia and level of a metabolite of noradrenalin, MHPG (3-methoxy 4-hydroxyphenyl glycol), and over-all the amnesic patients had MHPG levels that fell well below those of psychotic control patients. Unfortunately, there are serious doubts about the validity of the Wechsler Memory Scale, used in that study, which heretofore had been the only available measure of the severity of memory deficits (Walsh, 1978, pp. 317 ff.). Three of the tasks of the Wechsler Memory Scale have little, if anything, to do with the assessment of memory, and are more likely to reflect the level of arousal and orientation or the presence of dementia (speed of reciting the alphabet, counting backwards and successive addition). Another subtest, digit span, is usually normal in amnesic patients, and typically paired-associate memory for well established pairs is also good in such patients, whereas 'new' associates are poorly remembered. In our experience, also, some amnesic patients with good short-term memory can also perform adequately on memory for stories. Another subtest, memory for visual designs, is generally impaired in amnesic patients. Therefore, the details of the pattern of results on the subtests are more likely to be useful than the global score, which can be misleading, and patients who are undeniably amnesic clinically can score normally. McEntee and Mair classified a patient as amnesic only if there was a difference of at least 20 points between the intelligence quotient (WAIS) and the Wechsler memory quotient which, questions of validity aside, leads to the paradox that a patient with a memory quotient better than normal may nevertheless be classified as amnesic (which was actually the case with one of their subjects). Therefore, one cannot be certain whether the correlation reported by McEntee and Mair is with severity of *amnesia*, as such, but their study is noteworthy in attempting to use a quantitative measure of the psychological status and also in advancing a novel biochemical hypothesis. If the hypothesis is supported by further evidence, it might well turn out that biochemical assays, either of CSF or of brain tissue, would be more sensitive in some clinical conditions than changes seen with conventional histological neuropathological methods, and that the two sources of evidence could complement each other in important ways.

The two patients reported here were originally selected for study because clinically their amnesic defect seemed not only severe but relatively pure, that is, other cognitive capacities, as far as could be ascertained, were unimpaired. Their memory profiles were characteristic of a larger series of cases reported to us with varying ætiologies, but selected by the same criteria as far as psychological status was concerned. It is possible that selection by other criteria and for different aims, for example, for characterizing the general population of alcoholic patients diagnosed as having Korsakoff's psychosis, might yield broader or even qualitatively somewhat different profiles, even if the patients fall within normal levels of intelligence (but not necessarily unchanged from premorbid levels). For example, short-term memory scores of E.A. and H.J. were quite normal or even superior to normal, and this was true not only of our larger series of patients but also supports the earlier findings of Baddeley and Warrington (1970). In the Boston alcoholic Korsakoff series studied by Butters and Cermak (1975), short-term memory was reported to be defective. It is possible that seemingly slight but probably important differences in selection criteria might be reflected in different neuropathological findings. And while one cannot generalize from just two cases, it is noteworthy that the mild intellectual loss in E.A. (which was significant but whose WAIS full scale IQ of 91 nevertheless was just within the average range and who therefore would have been included in a typical non-longitudinal series) was associated with more widespread brain damage than seen in the other patient, whose intellectual status was quite stable.

Both E.A. and H.J. showed not only a severe impairment in anterograde recognition memory, scoring at chance with forced-choice recognition of both faces and words, but they also displayed a severe retrograde amnesia for recall of events antedating their illness by a period of at least twenty-five years. Both subjects also showed the characteristic differential improvement in retention scores when tested by cued recall, and both also showed the characteristic 'prior learning effect' in a cued recall reversal learning paradigm, that is they showed excellent retention of the first list of items, but a marked inability to acquire a second list which shared the same cues as the first list. Whatever theoretical interpretation one places on this constellation of results (*see* Weiskrantz and Warrington, 1975, for review), it seems reasonable to consider the relatively restricted pathological loci as forming a link in a circuit necessary for long-term memory processing rather than as constituting the repository of stored items as such, or even the simple output from such a store. The mammillary bodies are a narrow funnel through which connections from the midbrain as well as the temporal lobe neocortex and limbic system gain access to the frontal lobes. In man the fornix mammillothalamic system achieves a relatively large size in relation to the monkey (Powell, Guillery and Cowan, 1957; *see* Krieckhaus, 1967), and lesions in it must cause a major disconnection. There still may remain, however, parallel pathways that can bypass the disconnection—for example, the temporal neocortex projects along a multi-synaptic pathway to amygdala and thence probably to midline thalamus and thence to the orbital frontal cortex, although this pathway may normally be involved in a different type of memory processing than that of the fornix-mammillary system (*see* Gaffan, 1976, for a discussion of the dissociation of recognition and associative types of memory). Perhaps the importance of pathology in the midline thalamic region, when found in conjunction with that in the mammillary bodies, lies in interrupting parallel pathways, hence making the disconnection more complete and the amnesic phenomena more profound and enduring.

SUMMARY

Neuropathological findings in the brains of two alcoholic patients with Korsakoff's psychosis are reported. Their memory defects had been studied in detail quantitatively over a period of nine years in one case and three years in the other, relevant details of which are presented. Both patients had had a relatively pure long-term memory impairment in the absence of other cognitive deficits and in the absence of a short-term memory impairment. Their retrograde amnesia for public events and famous faces had been measured and found to have extended backwards over at least twenty-five years. There was severe impairment in anterograde recognition memory for both verbal and non-verbal material. On a newly prepared memory quotient battery both patients had scored well below the bottom of the normal scale (< 60, where 100 is the mean with a standard deviation of ±15). Both patients had also shown the characteristic differential improvement in retention when tested by cued recall and also the characteristic 'prior learning effect',

i.e. normal retention of one list of words when tested by cued recall but impaired retention of a second list sharing the same cues as the first list. There had been a slight but significant deterioration in intelligence in one of the patients in the two years prior to his death, although his IQ still fell within the normal range. The other patient remained undeteriorated until his death, and his IQ also was close to an estimated measure of his premorbid IQ.

In the brains of both patients there was marked gliosis, shrinkage and discolouration bilaterally in the medial nuclei of the mammillary bodies. In addition there was a thin band of gliosis bilaterally between the wall of the third ventricle and the medial dorsal nucleus, the rostral limit lying anterior to the medial dorsal nucleus. In the patient with no intellectual deterioration these were the only pathological changes that were seen. In neither patient was there evident local loss of nerve cells, gliosis or any other qualitative evidence of abnormality in the hippocampi, the white matter of the temporal lobes or the greater part of the medial dorsal nuclei, although it is difficult to be certain whether there was any overlap between the band of gliosis and the most medial region of the medial dorsal nucleus and other adjacent thalamic nuclei. In the other patient there was also a small zone of softening in the cerebellum and an increase in astrocytes in other regions of the cerebral hemispheres, including the basal ganglia, amygdala, and brain-stem, but without noticeable loss of cells. The question of the minimal lesion for the alcoholic Korsakoff amnesic state, and some aspects of the related anatomy, is discussed in the context of other reports in the literature which are, however, difficult to assess in the absence of details of the specificity, severity and character of the memory disorders.

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REFERENCES

Adams, R. D. (1969) The anatomy of memory mechanisms in the human brain. In: *The Pathology of Memory.* Edited by G. A. Talland and N. C. Waugh. New York and London: Academic Press, pp. 91–106.

—— Collins, G. H. and Victor, M. (1962) Troubles de la mémoire et de l'apprentissage chez l'homme; leurs relations avec des lésions des lobes temporaux et du diencéphale. In: *Physiologie de l'Hippocampe.* Paris: Centre National de la Récherche Scientifique, pp. 273–296.

Baddeley, A. D. (1975) Theories of amnesia. In: *Studies in Long-Term Memory.* Edited by A. Kennedy and A. Wilkes. London: Wiley, pp. 327–343.

BADDELEY, A. D. and WARRINGTON, E. K. (1970) Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behaviour*, **9**, 176–189.

BRIERLEY, J. B. (1977) Neuropathology of amnesic states. In: *Amnesia*. Edited by C. W. M. Whitty and O. L. Zangwill. London: Butterworths, pp. 199–223.

BUTTERS, N. and CERMAK, L. (1975) Some analyses of amnesic syndromes in brain-damaged patients. In: *The Hippocampus*. Vol. 2. *Neurophysiology and Behavior*. Edited by R. L. Isaacson and K. H. Pribram. New York and London: Plenum Press, pp. 377–409.

CAMPBELL, A. C. P. and BIGGART, J. H. (1939) Wernicke's encephalopathy (poliocephalitis hæmorrhagica superior); its alcoholic and non-alcoholic incidence. *Journal of Pathology and Bacteriology*, **48**, 245–262.

DELAY, J., BOUDIN, G., BRION, S. and BARBIZET, J. (1956) Étude anatomo-clinique de huit encéphalopathies alcooliques; encéphalopáthie de Gayet-Wernicke et syndrome Voisins. *Revue Neurologique*, **94**, 596–601.

—— and BRION, S. (1954) Syndrome de Korsakoff et corps mamillaires. *L'Encéphale*, **43**, 193–200.

—— —— (1969) *Le Syndrome de Korsakoff*. Paris: Masson.

—— —— and ELISSALDE, B. (1958*a*) Corps mamillaires et syndrome Korsakoff. Étude anatomique de huit cas de syndrome de Korsakoff d'origine alcoolique sans altérations significative du cortex cérebral. I. Étude anatomo-clinique. *Press Medicale*, **66**, 1849–1852.

—— —— —— (1958*b*) Corps mamillaires et syndrome Korsakoff. Étude anatomique de huit cas de syndrome de Korsakoff d'origine alcoolique sans altérations significative du cortex cérebral. II. Tubercules mamillaires et mécanisme de la mémoire. *Press Medicale*, **66**, 1965–1968.

FEREMUTSCH, K. and SIMMA, K. (1955) Structuranalysen des menschlichen thalamus. IV. Nucleus anterior, nucleus mediodorsalis, nucleus pulvinaris thalami. *Monasschrift für Psychiatrie und Neurologie*, **130**, 347–359.

FRY, W. J., KRUMINS, R., FRY, F. J., THOMAS, G., BORBELY, S. and ADES, H. (1963) Origins and distributions of some efferent pathways from the mammillary nuclei of the cat. *Journal of Comparative Neurology*, **120**, 195–257.

Functions of the Septo-Hippocampal System. (1978) Ciba Foundation Symposium 58 (new series). Amsterdam, Oxford, New York: Elsevier, Excerpta Medica, North Holland.

GAFFAN, D. (1976) Recognition memory in animals. In: *Recognition and Recall*. Edited by J. Brown. London: Wiley, pp. 229–242.

GAMPER, E. (1928) Zur Frage der Polioencephalitis haemorrhagica der chronischen Alkoholiker. Anatomische Befunde beim alkoholischen Korsakov und ihre Beziehungen klinischen bild. *Deutsche Zeitscrift für Nervenheilkunde*, **102**, 122–129.

GRUNER, J. E. (1956) Sur la pathologie des encéphalopathies alcooliques. *Révue Neurologique*, **94**, 682–689.

GUDDEN, H. (1896) Klinische und anatomische beiträge zur kenntnis der multiplen Alkoholneuritis nebst bemärkungen über die Regenerationsvorgänge in peripheren Nervensystem. *Archiv für Psychiatrie und Nervenkrankheiten*, **28**, 643–741.

GUILLERY, R. W. (1956) Degeneration in the post-commissural fornix and the mammillary peduncle of the rat. *Journal of Anatomy, London*, **90**, 350–370.

HIERONS, R., JANOTA, I. and CORSELLIS, J. A. N. (1978) The late effects of necrotizing encephalitis of the temporal lobes and limbic areas: a clinico-pathological study of 10 cases. *Psychological Medicine*, **8**, 21–42.

HOREL, J. A. (1978) The neuroanatomy of amnesia: a critique of the hippocampal memory hypothesis. *Brain*, **101**, 403–445.

KANT, F. (1932) Die pseudoencephalitis Wernicke der alkoholiker (Polioencephalitis haemorrhagica superior acuta). Ein beitrag zur klinik der alkoholpsychosen. *Archiv für Psychiatrie und Nervenkrankheiten*, **98**, 702–768.

KENNEDY, C., SAKURADA, O., SHINOHARA, M., JEHLE, J. and SOKOLOFF, L. (1978) Local cerebral glucose utilization in the normal conscious macaque monkey. *Annals of Neurology*, **4**, 293–301.

KIEVIT, J. and KUYPERS, H. G. J. M. (1977) Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. *Experimental Brain Research*, **29**, 299–322.

KRETTEK, J. E. and PRICE, J. L. (1977) The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *Journal of Comparative Neurology*, **171**, 157–191.

KRIECKHAUS, E. E. (1967) The mammillary bodies: their function and anatomical connections. *Acta Biologiae Experimentalis, Warsaw*, **27**, 319–337.

KUHLENBECK, H. (1954) The human diencephalon. *Confinia Neurologica*, **14**, Supplement, 1–230.

MCENTEE, W. J., BIBER, M. P., PERL, D. P. and BENSON, D. F. (1976) Diencephalic amnesia: a reappraisal. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 436–441.

—— and MAIR, R. G. (1978) Memory impairments in Korsakoff's psychosis: a correlation with brain noradrenergic activity. *Science*, **202**, 905–907.

MALAMUD, N. and SKILLICORN, S. A. (1956) Relationship between the Wernicke and Korsakoff syndrome. *Archives of Neurology and Psychiatry, Chicago*, **76**, 585–596.

MISHKIN, M. (1978) Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature, London*, **273**, 297–298.

NELSON, H. E. and O'CONNELL, A. (1978) Dementia: the estimation of premorbid intelligence levels using the new adult reading test. *Cortex*, **14**, 234–244.

ÖRTHNER, H. VON (1957) Pathologische Anatomie der vom Hypothalamus ausgelösten Bewusstseinsstörungen. In: *Premier Congrès International des Sciences Neurologiques*. Edited by L. van Bogaert and J. Radernecker. London: Pergamon Press, vol. II, pp. 77–96.

POWELL, T. P. S., GUILLERY, R. W. and COWAN, W. M. (1957) A quantitative study of the fornix-mamillo-thalamic system. *Journal of Anatomy, London*, **91**, 419–437.

REMY, M. (1942) Contribution à l'étude de la maladie de Korsakov. Étude anatomo-clinique. *Monatsschrift für Psychiatrie und Neurologie*, **106**, 128–144.

RIGGS, H. E. and BOLES, H. S. (1944) Wernicke's Disease: a clinical and pathological study of 42 cases. *Quarterly Journal of Studies in Alcohol*, **5**, 361–370.

SANDERS, H. I. and WARRINGTON, E. K. (1971) Memory for remote events in amnesic patients. *Brain*, **94**, 661–668.

SCOVILLE, W. B. and MILNER, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **20**, 11–21.

SOKOLOFF, L., REIVICH, M., KENNEDY, C., DES ROSIERS, M. H., PATKAK, C. S., PETTIGREW, K. D., SAKURADA, O. and SHINOHARA, M. (1977) The (^{14}C) deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, **28**, 897-916.

SPIEGEL, E. A., WYCIS, H. T., ORCHINIK, L. W. and FREED, H. (1955) The thalamus and temporal orientation. *Science*, **121**, 771-772.

TALLAND, G. (1965) *Deranged Memory*. New York: Academic Press.

TSIMINAKIS, Y. (1931) Beitrag zur pathologie der alkoholischen erkrankungen der centralnervensystems. *Arbeiten auf dem neurologischen Institute an der Wiener Universität*, **33**, 24–62.

VALENSTEIN, E. S. and NAUTA, W. J. H. (1959) A comparison of the distribution of the fornix system in the rat, guinea pig, cat and monkey. *Journal of Comparative Neurology*, **113**, 337-363.

VAN BUREN, J. M. and BORKE, R. C. (1972) *Variations and Connections of the Human Thalamus*. Vols. I and II. Berlin, Heidelberg, New York: Springer-Verlag.

VICTOR, M., ADAMS, R. D. and COLLINS, G. H. (1971) *The Wernicke-Korsakoff Syndrome*. Oxford: Blackwell.

WALSH, K. W. (1978) *Neuropsychology*. Edinburgh, London and New York: Churchill Livingstone.

WARRINGTON, E. K. (1974) Deficient recognition memory in organic amnesia. *Cortex*, **10**, 289-291.

—— and WEISKRANTZ, L. (1968) A new method of testing long-term retention in amnesic patients. *Nature, London*, **217**, 972-974.

—— —— (1973) An analysis of short-term and long-term memory defects in man. In: *The Physiology of Memory*. Edited by J. A. Deutsch. New York and London: Academic Press, pp. 365-395.

—— —— (1974) The effect of prior learning on subsequent retention in amnesic patients. *Neuropsychologia*, **12**, 419-428.

—— —— (1978) Further analysis of the prior learning effect in amnesic patients. *Neuropsychologia*, **16**, 169-176.

WEISKRANTZ, L. and WARRINGTON, E. K. (1975) The problem of the amnesic syndrome in man and animals. In: *The Hippocampus*. Vol. 2. *Neurophysiology and Behavior*. Edited by R. L. Isaacson and K. H. Pribram. New York and London: Plenum Press, pp. 411–428.

WERNICKE, C. (1881) *Lehrbuch der Gerhirnkrankheiten*. Vol. II. Berlin: Theodore Fischer, p. 229.

WHITE, J. C. and COBB, S. (1955) Psychological changes associated with giant pituitary neoplasms. *Archives of Neurology and Psychiatry, Chicago*, **74**, 383-396.

WILLIAMS, M. and PENNYBACKER, J. (1954) Memory disturbance in third ventricle tumours. *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 115-123.

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Brain (1979), **102**, 785-804

VESTIBULAR SUPPRESSION IN PERIPHERAL AND CENTRAL VESTIBULAR DISORDERS

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INTRODUCTION

ACCORDING to Feldman and Bender (1969) one of the greatest defects of the caloric test described by Fitzgerald and Hallpike (1942) is the insistance that it should be carried out in the presence of optic fixation. This they maintain 'should be modified so that testing is performed in darkness or with eyes closed'. Removal of optic fixation, of course, normally considerably enhances the nystagmic response and the presumption is that the test will be made appreciably more sensitive. With the introduction of electronystagmography this now presents no problem and in addition there is the further advantage that the resultant recording provides a permanent record of the responses which can be analysed in respect of a number of useful parameters such as nystagmus frequency, slow component velocity, and duration.

Unfortunately as Demanez and Ledoux (1970) have pointed out, the results of the two techniques, testing with and without fixation, are by no means comparable and important discrepancies have appeared in recent literature.

These may be explained on a number of counts (Dix and Hood, 1973; Hood, 1977) but Demanez and Ledoux have elaborated at length on one particular aspect, namely the differential effect of the removal of optic fixation upon the nystagmic response according to the level of the lesion within the CNS, and have indeed shown that this might in itself have useful clinical application.

Demanez and Ledoux carried out caloric tests on three groups of subjects, normal subjects, patients with peripheral vestibular lesions and patients with central vestibular lesions. Each irrigation began with eyes closed. Seventy seconds after the beginning of irrigation the eyes were opened and an assessment made of the inhibiting effect of fixation in terms of a fixation index expressed as

$$\frac{\text{amplitude of nystagmic beats} \times \text{frequency (eyes open)} \times 100}{\text{amplitude of nystagmic beats} \times \text{frequency (eyes closed)}}$$

They found that whereas the fixation index fell between 8 and 25 per cent in both normal subjects and patients with peripheral vestibular involvement the group with miscellaneous neurological disorders were largely grouped between 25 and 80 per cent, some of them even exceeding 200 per cent. In other words the relative inhibitory effect of optic fixation was considerably less marked in the group with central lesions than in the other two. Similar results have been reported by Corvera, Somante, Torres and Lopez (1968) and Boniver and Demanez (1977).

Although, therefore, this serves to emphasize the non-comparability of the conventional caloric tests and tests involving electronystagmography it raises the possibility that applied in this way, the latter could provide important supplementary information.

However, more recently, Tjernström (1973) has been particularly critical of the use of eye closure as a means of removing optic fixation, maintaining that the nystagmic response is especially susceptible to the subject's state of arousal. Furthermore, he has demonstrated clearly that Bell's phenomenon (elevation of the eyes behind closed lids) may intervene and at times completely suppress the response. The result of both these factors would be a significant modifying effect upon the fixation index unrelated to the underlying pathology.

A reappraisal of the situation is clearly called for. Quite apart from the question of the unpredictable effects of eye closure, more information is needed on the mechanisms underlying the fixation index. Thus, for example, the high fixation indices in central lesions could result equally well from a relative reduction of the response during eye closure as from an enhancement of the response in the presence of optic fixation.

The present investigation has been carried out with a view to clarifying these and other problems. As a result it now seems possible to develop a hypothesis of the nervous mechanisms underlying the suppressive effects of optic fixation in both peripheral and central lesions which accords well with all the available clinical, anatomical and physiological data.

METHOD

Three groups of subjects were selected for study, 10 normal subjects with no history of vestibular disorder, 13 patients with peripheral vestibular lesions and 9 patients with miscellaneous neurological disorders. The clinical diagnosis of the patients is listed in Table 1.

Caloric tests according to the manner prescribed by Fitzgerald and Hallpike (1942) were carried out on each subject on separate occasions. On the first occasion the subject was required to fixate a

TABLE 1

PERIPHERAL VESTIBULAR LESIONS		CENTRAL LESIONS	
No.	*Diagnosis*	*No.*	*Diagnosis*
11	Unilateral Ménière's disease	4	Multiple sclerosis
1	Viral infection	2	Brain-stem lesion
1	Traumatic labyrinthine concussion	1	Meningioma in cerebellopontine angle
		1	VIIIth nerve neurofibroma
		1	Cerebellar hæmangioma

target immediately above his head throughout the course of the test. On the second occasion, immediately following irrigation, the lights were turned out and the subject remained in total darkness with the eyes open for the remainder of the test.

In this way we were able to make direct comparison of the responses in the presence or absence of optic fixation without the possibly contaminating effects of one upon the other. Furthermore, the use of total darkness instead of eye closure as a means of removing optic fixation served to eliminate the uncertainties associated with the latter.

Eye movements were recorded electronystagmographically on an Elema Mingograph using D.C. amplification, calibration between targets 30 degrees to the left and right of the midline being carried out immediately before and following each test. In addition a special facility developed in the Unit (Trinder, 1975) made possible the on-line computation of the slow component velocity of the nystagmic response to each irrigation. This was displayed upon an XY Plotter.

RESULTS

Examples typical of the responses of the subjects in each group are given in figs. 1, 2 and 3. Also shown are tracings of the nystagmus occurring during the ten-second period approximating to the culmination of the response both in darkness and in the presence of optic fixation.

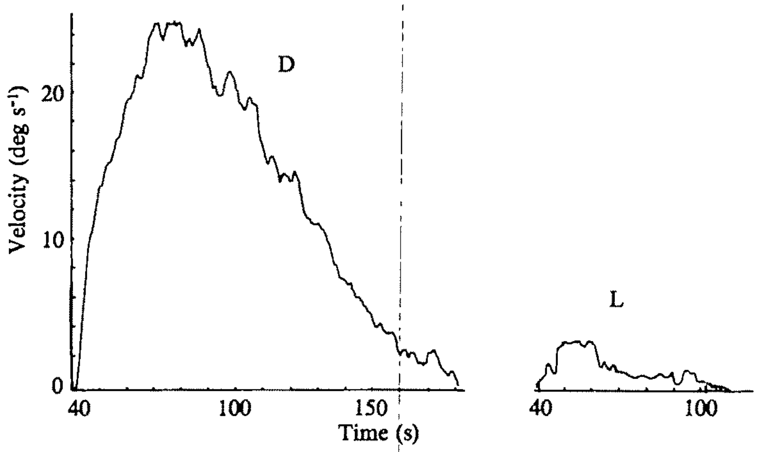

FIG. 1A. Traces of computed slow component velocity of nystagmic response to caloric irrigation carried out in darkness (*D*) and in the light (*L*). Normal subject.

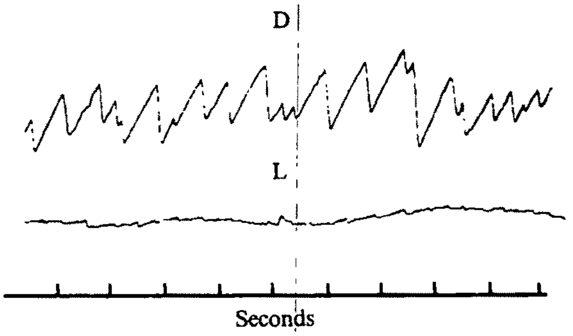

FIG. 1B. Tracings of nystagmus at the culmination of the responses in A; darkness (*D*), light (*L*).

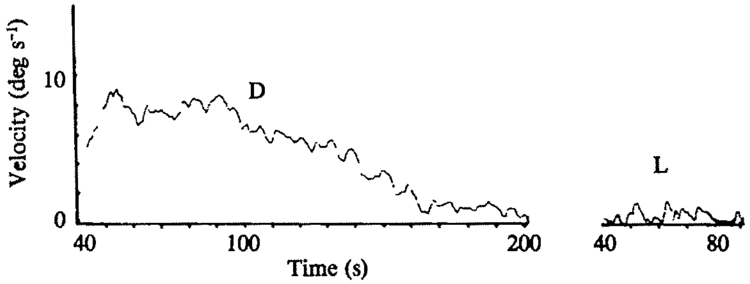

FIG. 2A. Traces of computed slow component velocity of nystagmic response to caloric irrigation carried out in darkness (*D*) and in the light (*L*). Patient with peripheral vestibular lesion.

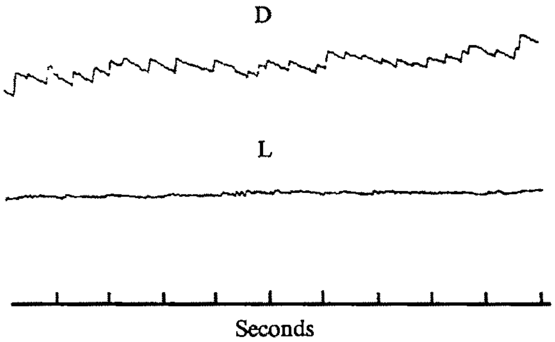

FIG. 2B. Tracings of nystagmus at the culmination of the responses in A; darkness (*D*), light (*L*).

From data of this kind measurements were made of (*a*) the latent period of the response from the beginning of irrigation; (*b*) the duration of the response; (*c*) the culmination of the response; (*d*) maximum slow phase velocity and (*e*) maximum nystagmus beat frequency. The results from the three groups are presented in Tables 2, 3 and 4 and summarized in respect of their mean values in Table 5. The latter data is embodied for convenience of discussion in the schematic representations of the responses in the three respective groups shown in fig. 4.

Concerning first the duration of the responses it will be seen that both in the presence and absence of optic fixation the average durations of the responses of the peripheral group approach those of the normal group. In both groups, removal of optic fixation results in a striking enhancement of the duration of the response, in effect by a factor of 2. By contrast, in respect of the central group the duration in the presence of optic fixation is significantly greater than that of the normal group but very little increased in darkness.

This finding provides striking experimental justification for a somewhat empirical practice which has been in use for some years now in our clinics at Queen Square in which, following the termination of the conventional caloric response as determined by direct observation of the eyes, the patient is put into total darkness and the eyes observed under infra-red illumination with a viewer. With this procedure it has been our general experience that in the case of peripheral vestibular lesions the nystagmic response reappears and is much prolonged, whereas in the case of central lesions either no or very slight nystagmus of short duration becomes evident.

Observations of this kind supplementary to the conventional caloric tests have been found to have particular application in the differential diagnosis of lesions of the peripheral and central vestibular pathways and are now carried out routinely.

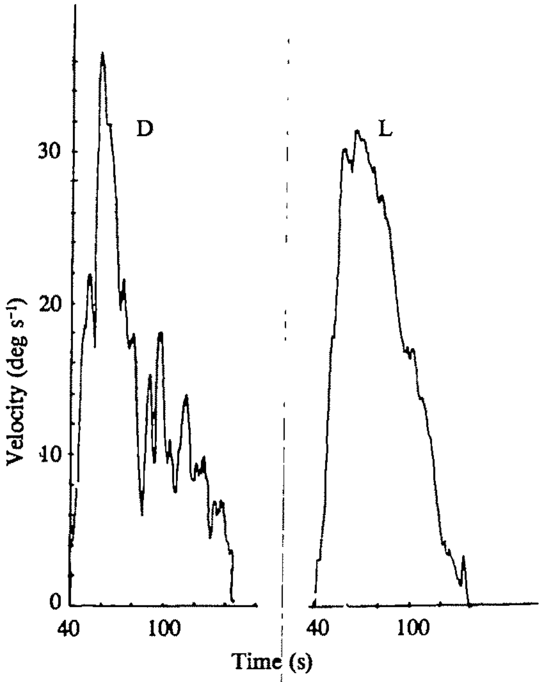

FIG. 3A. Traces of computed slow component of nystagmic responses to caloric irrigation carried out in darkness (*D*) and in the light (*L*). Patient with central vestibular lesion.

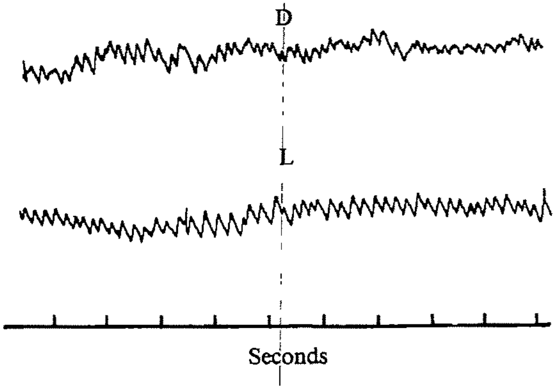

FIG. 3B. Tracings of nystagmus at the culmination of the responses in A; darkness (*D*), light (*L*).

TABLE 2. NORMAL SUBJECTS

Case No.	*Fixation/ No fixation*	*Stimulus*	*Ear*	*Duration of response, seconds*	*Latency from start of irrigation, seconds*	*Period of culmination, seconds*	*Maximum slow phase velocity, deg s^{-1}*	*Maximum beat frequency, Hz*
1	Fixation	Hot	L	120	40	65–75	3.5	2.7
			R	120	40	65–75	3	2.6
	No fixation	Hot	L	240	—	75–85	37	2.6
			R	240	—	80–90	48	2.5
2	Fixation	Cold	L	115	35	65–75	7	2.9
			R	110	35	65–75	5	2.6
	No fixation	Cold	L	190	—	70–80	36	2.4
			R	185	—	65–75	27	2.7
3	Fixation	Cold	L	90	50	65–75	1	2.3
			R	90	45	65–75	1.5	2.2
	No fixation	Cold	L	155	—	70–80	8	2.7
			R	160	—	70–80	11	3.0
4	Fixation	Hot	L	95	45	70–80	2	1.4
			R	105	45	70–80	3	1.8
	No fixation	Hot	L	185	—	75–85	23	1.3
			R	190	—	80–90	21	1.7
5	Fixation	Hot	L	120	40	65–75	2.5	1.3
			R	120	40	65–75	4	1.6
	No fixation	Hot	L	240	—	65–75	14	2.5
			R	240	—	65–75	27	3.1
6	Fixation	Cold	L	110	40	65–75	3	2.1
			R	110	40	60–70	3	2.3
	No fixation	Cold	L	180	—	65–75	24	1.9
			R	175	—	70–80	28	2.2
7	Fixation	Cold	L	100	50	65–75	1	1.0
			R	100	50	65–75	1	1.3
	No fixation	Cold	L	240	—	80–90	11	1.7
			R	230	—	75–85	10	2.2
8	Fixation	Hot	L	105	45	60–70	2.5	1.9
			R	120	35	60–70	8.5	3.1
	No fixation	Hot	L	190	—	70–80	24	3.3
			R	190	—	70–80	35	3.3
9	Fixation	Cold	L	105	40	70–80	3.5	1.9
			R	105	40	70–80	3.5	2.0
	No fixation	Cold	L	180	—	80–90	24	2.5
			R	180	—	80–90	18	2.1
10	Fixation	Hot	L	105	40	65–75	3	2.0
			R	105	40	65–75	3	2.0
	No fixation	Hot	L	190	—	70–80	23	2.4
			R	190	—	70–80	27	2.5

TABLE 3. PERIPHERAL LESIONS

Case No.	*Side of lesion*	*Fixation/ No fixation*	*Stimulus*	*Ear*	*Duration of response, seconds*	*Latency from start of irrigation, seconds*	*Period of culmination, seconds*	*Maximum slow phase velocity, deg. s⁻¹*	*Maximum beat frequency, Hz*
1	L	Fixation	Cold	L	Nil	—	—	—	—
				R	90	50	60–70	1.5	2.3
		No fixation	Cold	L	210	—	70–80	3.5	1.0
				R	220	—	70–80	16	3.2
2	R	Fixation	Hot	L	120	50	70–80	2	1.5
				R	80	50	70–80	0.5	9.0
		No fixation	Hot	L	230	—	75–85	24	2.5
				R	220	—	80–90	12	1.5
3	L	Fixation	Hot	L	Nil	—	—	—	—
				R	120	45	65–75	3	1.6
		No fixation	Hot	L	180	—	80–90	4	1.4
				R	180	—	75–85	22	3.8
4	R	Fixation	Hot	L	130	35	60–70	3	2.3
				R	90	55	60–70	0.25	8.0
		No fixation	Hot	L	205	35	60–70	24	3.2
				R	205	—	60–70	8	2.5
5	L	Fixation	Hot	L	Nil	—	—	—	—
				R	90	50	65–75	1	1.1
		No fixation	Hot	L	130	—	60–70	4	1.5
				R	140	—	65–75	8	2.0
6	R	Fixation	Hot	L	110	35	60–70	12	3.1
				R	95	50	65–75	0.5	9.0
		No fixation	Hot	L	170	35	65–75	49	3.0
				R	170	—	65–75	10	2.2
7	L	Fixation	Cold	L	90	45	65–75	0.5	1.1
				R	120	40	65–75	3	2.2
		No fixation	Cold	L	200	—	65–75	12	2.1
				R	200	—	65–75	29	2.7
8	R	Fixation	Cold	R	73	60	60–70	1	8.0
		No fixation	Cold	R	190	—	70–80	14	3.1
9	R	Fixation	Hot	R	108	58	60–70	1.5	1.2
		No fixation	Hot	R	180	—	80–90	18	2.1
10	R	Fixation	Cold	R	150	25	60–70	1	9.0
		No fixation	Cold	R	175	—	75–85	15	3.2
11	L	Fixation	Hot	L	100	40	60–70	0.75	3.0
		No fixation	Hot	L	124	—	70–80	15	2.0
12	L	Fixation	Hot	L	160	40	60–70	1	1.0
		No fixation	Hot	L	—	—	50–60	16	2.3
13	R	Fixation	Hot	R	93	48	60–70	2	7.0
		No fixation	Hot	R	175	—	70–80	18	1.8

TABLE 4. CENTRAL LESIONS

Case No.	*Fixation/ No fixation*	*Stimulus*	*Ear*	*Duration of response, seconds*	*Latency from start of irrigation, seconds*	*Period of culmination, seconds*	*Maximum slow phase velocity, deg s^{-1}*	*Maximum beat frequency, Hz*
1	Fixation	Hot	L	145	30	65–75	11	4.9
			R	135	30	65–75	31	5.1
	No fixation	Hot	L	155	—	60–70	22	3.1
			R	145	—	60–70	36	5.2
2	Fixation	Hot	L	135	25	60–70	7	3.9
			R		Absent responses			
	No fixation	Hot	L	125	—	60–70	5	1.8
			R		Absent responses			
3	Fixation	Cold	L	145	30	65–75	9	3.1
			R	145	30	65–75	6	3.0
	No fixation	Cold			Not done			
		Hot	L	140	30	65–75	8	2.8
			R	150	30	65–75	10	2.9
	No fixation	Hot			Not done			
4	Fixation	Cold	L	110	50	60–70	2	0.8
			R	135	20	55–65	8.5	4.4
		Hot	R	140	20	60–70	20.5	4.9
	No fixation	Cold	L	80	—	50–60	3	1.4
			R	135	—	55–65	14	2.2
		Hot	R	200	—	65–75	35	2.9
5	Fixation	Cold	L	120	50	65–75	1.5	0.9
			R	140	20	60–70	8	3.6
	No fixation	Cold	L	200	—	70–80	3	1.7
			R	200	—	60–70	21	3.0
6	Fixation	Cold	L	180	20	65–75	15	2.9
			R	160	20	65–75	9	2.9
	No fixation	Cold	L	150	—	60–70	6	3.2
			R	160	—	60–70	8	3.2
7	Fixation	Cold	L	110	35	55–65	7	3.0
			R	120	35	60–70	9	3.4
	No fixation	Cold	L	190	—	70–80	35	3.0
			R	215	—	65–75	40	2.8
8	Fixation	Cold	L	130	20	60–70	16	2.9
			R	140	20	65–75	70	4.3
		Hot	L	140	15	65–75	52	3.5
			R	135	20	65–75	16	4.1
	No fixation				Not done			
9	Fixation	Hot	L	140	30	65–75	7	3.3
			R	150	30	65–75	10	3.4
	No fixation	Hot	L	160	—	60–70	8	3.4
			R	175	—	60–70	11	3.2

TABLE 5. AVERAGE VALUES

		Normal		*Peripheral*		*Central*	
		Range	*Mean*	*Range*	*Mean*	*Range*	*Mean*
Duration (seconds)	Light	(90–120)	107.5	(73–160)	103.9	(110–180)	138.4
	Darkness	(155–240)	198.5	(124–220)	179.9	(80–215)	163.6
Culmination (seconds)	Light	(65–75)	70.3	(65–75)	67.0	(60–70)	67.7
	Darkness	(70–85)	77.3	(55–85)	73.8	(55–75)	66.1
Max. Velocity (deg s^{-1})	Light	(1–8.5)	3.2	(0.25–2)	0.9	(1.5–70)	15.2
	Darkness	(8–48)	23.8	(3.5–18)	11.5	(3–40)	17.6
Beat frequency (Hz)	Light	(1.0–3.1)	2.05	(0.1–1.2)	0.77	(0.8–5.1)	3.34
	Darkness	(1.3–3.3)	2.43	(1.0–3.2)	2.05	(1.4–5.2)	2.86
Latency (seconds)	Light	(35–50)	41.8	(25–60)	47.1	(15–50)	27.7

An additional observable feature of central lesions, however, is an obvious enhancement of the nystagmic response in the presence of optic fixation both in respect of frequency and amplitude and this, too, is clearly reflected both in the Tables and the schematic representation. Thus it will be seen that the average beat frequency of the central group attains a value at culmination of 3.34 s^{-1} in the presence of optic fixation and this surprisingly is reduced somewhat to 2.86 s^{-1} in darkness. This contrasts with values of 0.77 and 2.05 s^{-1} respectively in the peripheral group and 2.05 and 2.43 s^{-1} in the normal subjects. Similarly the maximum slow component velocities of the central group are abnormally high at 15.2 deg s^{-1} in the presence of optic fixation and only slightly increased

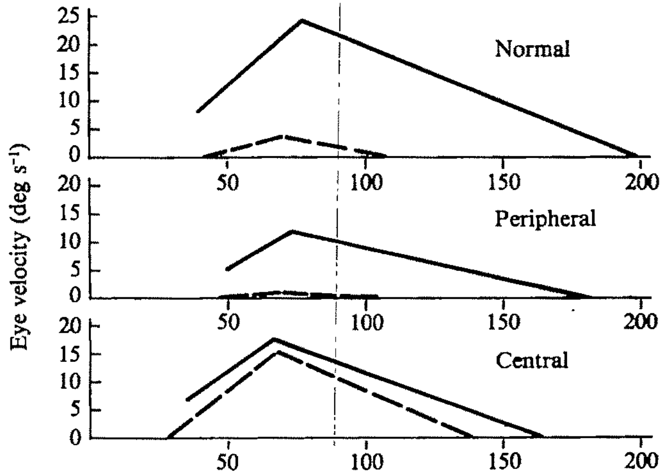

FIG. 4. Schematic representation of caloric responses in terms of eye velocity in normal subjects and patients with peripheral and central vestibular disorders. Full line = responses in darkness. Interrupted line = responses in the presence of optic fixation.

to 17.6 deg s^{-1} in darkness. Comparable values for the peripheral group and normal subjects are 0.9 and 11.5 deg s^{-1} and 3.2 and 23.8 deg s^{-1} respectively. It is thus abundantly clear that the high fixation indices reported by Demanez and Ledoux as being characteristic of central lesions have resulted primarily from a striking failure of fixation to suppress the vestibularly induced nystagmus. By contrast the overall response in darkness is smaller than that of normal subjects.

In order to gain some insight into the mechanisms subserving the suppressive effects of optic fixation upon the vestibular response in central and peripheral lesions we have adopted a somewhat different approach to that of Demanez and Ledoux, taking as our fixation index the ratio of the average slow component velocity during a ten-second period at the culmination of the response in darkness over the comparable value in the presence of optic fixation. This of course results in an inversion of Demanez and Ledoux's values. The relevant data are given in Tables 2, 3 and 4. In the case of peripheral lesions the responses in the presence of optic fixation were at times below the registration capabilities of the equipment and accordingly the slow component velocities were measured by hand with a specially designed cursor which made possible a resolution of one-quarter of a degree. On three occasions the responses, although detectable by eye, were not measurable and to these were assigned arbitrary values of 0.1 deg s^{-1}. The fixation indices established in this way in the three groups are listed in Table 6. The values at the unaffected ear in the case of unilateral peripheral lesions are also shown. Small errors in measurement in slow component velocities below 1 deg s^{-1} will, of course, give rise to large errors in the fixation indices and it has to be admitted that

TABLE 6. FIXATION INDICES

Case	*Normal subjects*		*Peripheral lesions*		*Central lesions*	
No.	*L. ear*	*R. ear*	*Normal ear*	*Impaired ear*	*L. ear*	*R. ear*
1	10.6	16	10.7	35	2	1.2
2	5.1	5.4	12	24	0.7	—
3	8	7.3	7.3	40	—	—
4	11.5	7	8	32	1.5	1.6, 1.7
5	5.6	6.8	8	40	2	2.6
6	8	9.3	4.1	20	0.4	0.9
7	11	10	9.7	24	5	4.4
8	9.6	4.1	—	14	—	—
9	6.9	5.1	—	12	1.1	1.1
10	7.7	9	—	15	—	—
11	—	—	—	20	—	—
12	—	—	—	16	—	—
13	—	—	—	9	—	—
Mean	8.2		8.5	23.2	1.9	
Standard deviation	2.73		2.39	10.13	1.29	

Infinite fixation indices would result in the case of the 3 patients with peripheral lesions who had no response in the light and in consequence these are not included in Table 6.

very high values of fixation indices may be in error by as much as 25 per cent. Nevertheless, it is abundantly clear that marked systematic differences are apparent.

Whereas the average value of the fixation index of normal subjects is of the order of 8, that of the central group is 2 and of the peripheral group 23. A test of significance between the means using the d statistic following the Fisher Behrens distribution showed that the difference between the normal subjects and patients with peripheral and central lesions was significant at least at the 1 per cent level. The high values of the peripheral group contrast with the findings of Demanez and Ledoux, who, it will be recalled, found no difference between their normal and peripheral groups. The reason for this is by no means clear, but it could have resulted both from their use of eye closure instead of darkness as a means of removing optic fixation and their method of measuring the fixation index during the course of a single caloric stimulus.

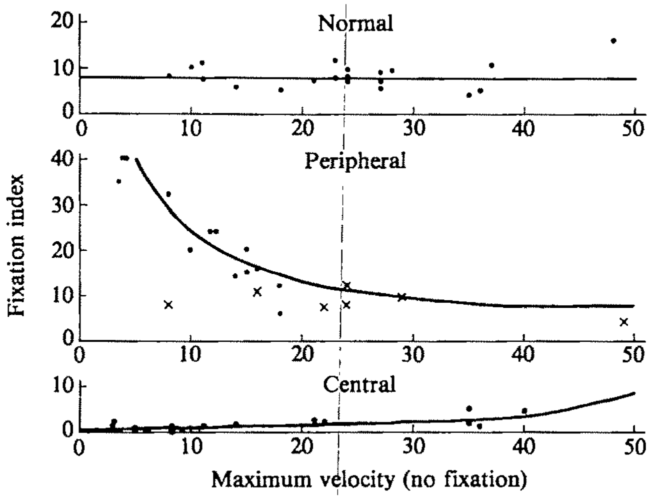

FIG. 5. Fixation indices in normal subjects and patients with peripheral and central vestibular disorders plotted as a function of maximum slow component velocity in darkness. The full line curves are derived from the hypothesis (*see text*). In the case of the peripheral lesions the crosses indicate responses from the normal ears.

In fig. 5 the individual results have been graphically displayed in terms of the relationship between the fixation indices and the maximum slow component velocities in darkness. Apart from the conspicuous differences in the magnitudes of the fixation indices in the three groups referred to above certain distinctive trends are clearly evident. Thus the fixation indices of the normal group remain scattered about a level of 8 for all maximum slow component velocities. In the peripheral group, however, high fixation indices are associated with low maximum slow component velocities, and as the latter increases the fixation indices approach the normal value. By contrast, in the central group extremely low values of fixation indices accompany low values of maximum slow component velocities and there is a slight but systematic increase of the fixation indices with increase in maximum slow component velocity.

It might, of course, be argued that irrespective of any underlying pathology the fixation indices are themselves a function of the slow component velocities in the light; hence the abnormally high values in respect of the peripheral group. While this seems unlikely in view of the fact that although the slow component velocities in the normal group covered a wide range, the fixation indices remained remarkably constant, we have, nevertheless, given the matter further consideration. To this end a pilot study was carried out upon three normal subjects.

Caloric tests were carried out in the light and in darkness on two occasions first with an irrigation of 40 s duration and second with one of 20 s duration. Despite the fact that the maximum slow component velocities were appreciably less with the 20 s irrigation, the fixation indices established from each pair of simuli, i.e. in light and in darkness, remained relatively unchanged. In view of these findings we feel confident that both the high values of fixation indices in respect of the peripheral group and the low values in respect of the central group are attributable to the underlying pathology.

DISCUSSION

By way of explanation of these findings it is pertinent to refer to the large body of evidence, both anatomical and physiological, which has now accumulated concerning the inhibitory control exerted by the cerebellum upon vestibulo-oculomotor function. Thus, according to recent studies (Brodal and Høivik, 1964), primary vestibular fibres terminate as mossy fibres in the flocculus, nodulus, uvula and paraflocculus, and most, if not all, are derived from the semicircular canals (Stein and Carpenter, 1967; Gacek, 1969). The cerebellum in turn has close anatomical connections with the vestibular nuclei and both also have fibre connections to the oculomotor nuclei. At the peripheral level, efferent fibres ending on the receptor cells have been identified and shown to differ structurally from the endings of the afferent processes (Kimura and Wersäll, 1962).

Although there appears to be numerous multisensory convergences upon these efferent inhibitory neurons (Llinás and Precht, 1969) there is clear evidence of cerebellar control (Llinás, Precht and Kitai, 1967). In consequence it can be assumed that optomotor-vestibular integration already takes place at the receptor level.

Of particular relevance to this discussion are the findings of Takemori and Suzuki (1978) that in monkeys, lesions of the fastigial and interpositus nuclei, the nodulus and uvula all give rise to a marked enhancement of the caloric responses while in addition Takemori and Cohen (1974) have demonstrated that visual suppression of caloric nystagmus is lost after extirpation of the flocculus. It is noteworthy in this respect that Noda, Asoh and Shibagaki (1977) have adduced clear evidence in the monkey that the flocculus sends tonic inhibitory impulses to eye movement neurons during fixation, and this aspect has been further elaborated upon in respect of the contribution the fovea makes to optokinetic nystagmus by Takemori and Suzuki (1977).

Taken together, this evidence strongly suggests that, in respect of vestibulo-optomotor function, cerebellar influence mediated by the vestibulo-cerebellar and optomotor pathways in the brain-stem has largely to do with the control of eye movements during fixation. If this is so then it would seem reasonable to suppose that optic fixation is an essential element of the overall response, and, as an important corollary, that when optic fixation is absent as, for example, when recordings are carried out in total darkness, then cerebellar influence, since it serves no useful purpose, is largely inactivated.

The validity of this supposition has in fact received convincing support from the recent studies of Lisberger and Fuchs (1977). These authors investigated the functional role of the flocculus in monkeys by recording the response of single unit potentials from Purkinje cells to sinusoidal angular rotation while the animals were either in darkness or performing a visual tracking task. They found that modulation of Purkinje cell activity occurred only during visual tracking and concluded accordingly that ‘Since the vestibular nerve excites and the flocculus inhibits vestibulo-ocular reflex (VOR) interneurons the two inputs should cancel, reducing the strength of the vestibular input reaching extra-ocular motor-neurons. During the VOR in the dark when the head and eye velocity inputs to the flocculus cancel and Purkinje cell firing is unmodulated, VOR interneurons would receive vestibular input only from the vestibular nerve, and the full strength of the vestibular nerve signal should be transmitted to extra-ocular motorneurons’. Upon this assumption a simple hypothesis can be put forward which provides a serviceable explanation of all the findings embodied in fig. 5.

Let us suppose the afferent discharge to have a value A at the culmination of the caloric response in darkness. For a variety of reasons the magnitude of the nystagmic response which this evokes will vary from one subject to another; hence the wide range of values found in normal subjects; and in consequence it is necessary to introduce a factor f which is an expression of this inter-subject variability. In any one subject, therefore, the nystagmus magnitude can be given as Af.

In the presence of optic fixation, however, the afferent discharge will be opposed by an efferent discharge E so that the resultant nystagmic response in light can be expressed as (A-E) f. The fixation index thus becomes:

$$\frac{\mathrm{Af}}{(\mathrm{A}\text{-}\mathrm{E})\,\mathrm{f}} = \frac{\mathrm{A}}{\mathrm{A}\text{-}\mathrm{E}} = 8 \text{ in the case of normal subjects.}$$

It can readily be seen, therefore, that E = 7/8 A or that the afferent response has a magnitude of 8 and the efferent, 7. Since the factor f reflects the wide range of normal values of maximum slow component velocities, the fixation index is invariant as indicated by the experimental values and the hypothesis.

When we come to consider the results on peripheral lesions a very different state of affairs emerges, since, although there is no reason to suppose that the magnitude of the cerebellar influence will be impaired, the afferent response will be reduced by different amounts according to the severity of the lesion. This, of course, is evident from the fact that the average nystagmic response in darkness is much reduced below the normal as shown in fig. 4. A clear indication of how this affects the fixation index can be obtained by substituting a range of values for A as follows:

Max. response in darkness Af	*Max. response in light* (A-E) f	*Fixation Index* $\frac{A}{A\text{-}E}$
8 f	(8–7) f = f	8
7.8 f	(7.8–7) f = 0.8 f	9.75
7.6 f	(7.6–7) f = 0.6 f	12.6
7.4 f	(7.4–7) f = 0.4 f	18.5
7.2 f	(7.2–7) f = 0.2 f	36

The resultant values for the fixation indices are shown to the right. As will be seen, the expectation is that as the afferent response falls the fixation indices rise precipitously. The full-line curve shown in fig. 5 is derived from these values and, as will be seen, provides a close approximation to the experimental values. Additionally, it can be presumed that when the afferent response falls below that of the efferent, i.e. a reduction of only 10 per cent or more, then the caloric response with fixation will be completely suppressed. Three such cases are listed in Table 3. It may seem surprising that such a small percentage reduction can be called in to account for the wide range of fixation indices in the peripheral group, yet it accords well with our clinical experience. Complete absence of response to one or more of the four caloric irrigations in the presence of fixation is extremely common in peripheral lesions, yet with the exception of those resulting from surgical intervention it is very rare not to be able to elicit a response, albeit of reduced magnitude, in darkness.

When we consider the central lesions the situation is quite different. Thus the peripheral response A will remain unimpaired at a value of 8 but the efferent discharge E mediated by way of the brain-stem will be reduced, again by varying amounts according to the severity of the lesion. Notional values are set out below together with the resultant fixation indices:

Max. response in darkness Af	*Max. response in light* (A-E) f	*Fixation Indices* $\frac{A}{A\text{-}E}$
8 f	(8–7) f = f	8
8 f	(8–5) f = 3 f	2.7
8 f	(8–3) f = 5 f	1.6
8 f	(8–1) f = 7 f	1.14

The hypothesis goes some way towards explaining both the enhanced response in the light and the abnormally low values of fixation indices. Furthermore, it will be seen that appreciable variations in the efferent discharge bring about only small changes to the fixation indices. This, however, is probably an over-simplification in respect of central lesions, because, if it were true, the caloric response curve in darkness shown in fig. 4 should be the same as that for normal subjects since it will represent the full unopposed receptor response. In fact, however, the maximum response falls somewhat short of the normal maximum, and this is further exemplified by the cluster of points to the left of the graph in fig. 5 with maximum values all below the range of normal values. It must, therefore, be presumed that some small reduction of the afferent discharge has occurred in all probability at the level of the vestibular nuclei.

If this is so, then the range of maximum slow component velocities along the abcissæ can be taken to express not only the inter-subject variability but also the extension of the lesion, with greatest to the left and least to the right. Upon this basis it would seem permissible to attempt to fit a curve of the form depicted by the hypothesis. As will be seen, good agreement is obtained with the experimental results.

It is, of course, a common finding in patients with central lesions, and those listed here are no exception, that they have impairment of visual tracking (i.e. optic fixation of a moving target), and in consequence it can be argued that they would have difficulty in generating an appropriate efferent signal to the oculomotor mechanism when retinal image movement is produced by an inappropriate vestibular afferent signal. In fact it seems highly unlikely that impaired pursuit and lack of suppression are directly related. In the first place we have examined pursuit in all the patients in the central group and found that although it was consistently deranged it varied from mild to gross impairment without any obvious correlation with the degree of suppression.

Of greater significance, however, are the results of pursuit studies we have subsequently carried out on a number of patients with similar central pathologies. In these the patients were required to track a moving light target both in darkness and against a striped background. To date, pursuit has been found to be appreciably more deranged with the background than in darkness; indeed in the latter situation we have frequently been unable to detect any abnormality despite the fact that gross abnormalities were present with the background. By contrast, Guedry, Davenport, Brewton and Turnispeed (1979) have recently shown that in normal subjects pursuit is better executed with a background than without.

Surprisingly, in the same patients we have found that when they were required to fixate upon the same light target attached to and rotating with a chair oscillating sinusoidally, suppression of the vestibulo-ocular reflex was better executed against the background than without. Quite clearly, these findings are not consistent with the notion that deranged tracking can be called in to account for the lack of vestibular suppression. It would seem rather that these are separate deranged mechanisms, and in the circumstances the most serviceable explanation for the lack of suppression, in accordance with our hypothesis, is removal or reduction of the efferent signal. It has, of course, to be admitted that the hypothesis is undoubtedly too simplistic and account needs to be taken of the more sophisticated and comprehensive models subserving the vestibulo-ocular reflex proposed by Robinson (1975), Raphan, Cohen and Matsuo (1977), and others. Nevertheless, it would seem to provide a starting point at least for reviewing one aspect of vestibulo-oculomotor function, namely cerebellar influence. In this connection it is instructive to consider one further application of the hypothesis. It is now well established that repeated rotation about the vertical axis results in a substantial reduction of the nystagmic responses. The phenomenon finds its most marked expression in ballet dancers and ice skaters and it has been customary to refer to it as vestibular habituation. In fact there are cogent reasons for supposing that in man, at any rate, it is not true habituation but is a manifestation of a more complex form of learning response (Hood, 1975). In any event there now exists a weighty body of evidence to show that the cerebellum is important for the occurrence of the phenomenon (Halstead, 1935; Halstead, Yacorzynski and Fearing, 1937) and in particular that the nodulus is implicated (Singleton, 1967; Wolfe, 1968). In a study on ballet dancers, Dix and Hood (1973), however, has shown that the reduction of the responses is specific to conditions involving optic fixation and that no reduction occurs to the rotational responses recorded in total darkness. In other words high fixation indices are a characteristic feature of these subjects' responses provoked either by rotational or caloric stimulation. They further demonstrated striking similarities between these subjects and certain patients with vestibular neuronitis, the presumption being (Hood, 1975) that in the latter group the same central mechanisms were invoked to suppress the pathological nystagmic movements of the eyes which would otherwise exacerbate the vertigo.

In the light of the above considerations, what clearly appears to have occurred, both in ballet dancers and vertiginous patients, is an augmentation of the cerebellar inhibitory influence upon optic fixation which is not present in darkness. This again can readily be accommodated by the hypothesis. Thus if we return to our normal values of 8 and 7 for the afferent and efferent responses, respectively, to caloric stimulation, it is necessary only to suppose that the latter is increased by some small amount, let us say to 7.5. The fixation index then becomes:

$$\frac{8\ \mathrm{f}}{(8\text{-}7.5)\ \mathrm{f}} = 16$$

With greater suppression the value of the fixation index will rise accordingly and in this respect it is interesting to note that Dix and Hood (1973) reported fixation indices as high as 80 in certain ballet dancers. High fixation indices are, of course, as has been reported earlier, a feature of peripheral vestibular lesions but these are presumed to arise not from an increase in efference but from a decrease in afference. In either event, however, the result is a relative increase in efference to afference which accounts for the high indices.

The overriding assumption inherent in all these considerations has been that cerebellar influence on vestibulo-oculomotor function has primarily to do with, and indeed is dependent upon, optic fixation. This inference is in accord with the notion which is currently gaining acceptance (Marr, 1969) that the cerebellum is, as it were, 'teachable' and that the development of automatic responses is dependent upon the structuring of complex neuronal circuitry which associates specific sensory activity with motor activity by way of Purkinje cells and their inputs from parallel fibres. Carpenter (1977) maintains that the evidence for such a process is particularly strong in respect of vistibulo-oculomotor function.

It follows that a learned response of this kind must be specific to particular sensory and motor inputs and in consequence it is difficult to see how any cerebellar influence can develop or be sustained in the absence of optic fixation. Needless to say this is only one aspect of cerebellar control. The functional significance of the efferent innervation of the vestibular system remains in large measure an enigma and doubtless involves a whole range of sensory inputs and associated motor control.

As to the clinical implications of these findings these would appear to be twofold. On the one hand caloric tests carried out in the manner described clearly have useful application in the differential diagnosis of central and peripheral vestibular lesions by revealing low fixation indices in the former and high in the latter. On the other hand the demonstration of striking differences in the caloric responses of peripheral and central lesions according to whether or not the tests are carried out in the presence or absence of optic fixation highlights the present controversy concerning the manner of administration of caloric tests which has arisen since the introduction of electronystagmography. Thus forceful suggestions have recently been put forward that in order to take advantage of the enhanced sensitivity recordings should be carried out either with eyes closed, in darkness, or behind Frenzel's glasses, in other words in the absence of optic fixation. Reference to fig. 4, however, will show that the advantages claimed may be more apparent than real. If we consider first the peripheral lesions; in darkness the durations of the responses approach those of the normal so that abnormalities present with optic fixation will tend to disappear. This in fact has recently been confirmed by Hood and Dix (1973). It can, of course, be argued that abnormalities still persist in respect of the slow component velocity and that measurement of this parameter is to be preferred. If, however, we turn to the central lesions the reverse is the case. In darkness the slow component velocity approaches the normal value as indeed does the overall response and the obvious enhancement in the presence of optic fixation so characteristic of central pathology has disappeared. Thus caloric tests carried out in the absence of optic fixation will eliminate, or reduce, evidence of pathology in peripheral lesions in respect of the duration of the responses and in central lesions in respect of the slow component velocity. By contrast abnormalities will persist in both during the course of optic fixation.

In the circumstances there would seem to be no compelling reasons at the present time for changing the manner of administration of the caloric test as described by Fitzgerald and Hallpike (1942) with its emphasis upon optic fixation. However, the addition of supplementary tests designed specifically for the determination of the fixation index could provide further valuable diagnostic information.

SUMMARY

Caloric tests have been carried out both in the presence of optic fixation and in total darkness upon normal subjects, patients with peripheral vestibular disorders and patients with central vestibular lesions. Nystagmic responses were recorded electronystagmographically and measurements made of latency and duration of response, maximum slow component velocity and beat frequency.

The relative enhancement of the response in darkness is expressed as a fixation index:

$$\frac{\text{maximum slow component velocity in darkness}}{\text{maximum slow component velocity with fixation}}$$

Compared to the normal group the peripheral group were found to have abnormally high fixation indices, the central group abnormally low. A hypothesis has been developed of the nervous mechanisms underlying the suppressive effects of optic fixation in both peripheral and central lesions which accords well with the available clinical, anatomical and physiological data.

The clinical implications of the findings are discussed both in respect of their localizing value and relevance to current innovations in the design of caloric tests.

REFERENCES

Boniver, R. and Demanez, J. P. (1977) Interest of the study of the influence of ocular fixation during caloric tests in ponto-cerebellar tumours. *ORL; Journal for Oto-Rhino-Laryngology and its Borderlands, Basel*, **39**, 203-208.

Brodal, A. and Høivik, B. (1964) Site and mode of termination of primary vestibulo-cerebellar fibres in the cat. An experimental study with silver impregnation methods. *Archives Italiennes de Biologie*, **102**, 1-21.

Carpenter, R. H. S. (1977) *Movements of the Eyes*. London: Pion Ltd., p. 303.

Corvera, J., Somante, R., Torres, G. and Lopez, R. G. (1968) Une nouvelle methode dans le diagnostic differential des lesions peripherique et des lesions central des voies vestibulo-oculomotrices. *Revue de Laryngologie d'Otologie et de Rhinologie*, **89**, 11-12.

Demanez, J. P. and Ledoux, A. (1970) Automatic fixation mechanisms and vestibular stimulation. *Advances in Oto-Rhino-Laryngology*, **17**, 90-98.

DIX, M. R. and HOOD, J. R. (1973) Vestibular habituation. Its clinical significance and relationship to vestibular neuronitis. *Laryngoscope*, **80**, 226–232.

FELDMAN, M. and BENDER, M. B. (1969) Neuro-opthalmology. Clinical tests of vestibular and oculomotor functions. In: *Progress in Neurology and Psychiatry*. Edited by E. A. Spiegel. London: William Heinemann, pp. 189–202.

FITZGERALD, G. and HALLPIKE, C. S. (1942) Studies in human vestibular function. 1. Observations on the directional preponderance (Nystagmusberietschaft) of caloric nystagmus resulting from cerebral lesions. *Brain*, **65**, 115–137.

GACEK, R. R. (1969) The course and central termination of first order neurons supplying vestibular end organs in the cat. *Acta Oto-Laryngologica, Stockholm*, Suppl. **254**, 1–66.

GUEDRY, F. E., DAVENPORT, K. S., BREWTON, C. B. and TURNISPEED, G. T. (1979) *The Pendular Eye Tracking Test under Two Background Viewing Conditions*. NAMRL 1257 Naval Aerospace. Medical Research Laboratory Pensacola, Florida.

HALSTEAD, W. C. (1935) The effects of cerebellar lesions upon habituation of post-rotatory nystagmus. *Comp. Psychol Monogr*, **42**, 1–130.

—— YACORZYNSKI, G. and FEARING, F. (1937) Further evidence of cerebellar influence in the habituation of after-nystagmus in pigeons. *American Journal of Physiology*, **120**, 350–355.

HOOD, J. D. (1975) The definition of vestibular habituation. In: *The Vestibular System*. Edited by R. Naunton. London and New York: Academic Press, pp. 219–224.

—— (1977) Whither vestibular tests? *Proceedings of the Royal Society of Medicine*, **70**, 675–678.

—— and DIX, M. R. (1973) The significance of optic fixation in tests of vestibular function. *Equilibrium Research*, **3**, 95–101.

KIMURA, R. and WERSÄLL, J. (1962) Termination of the olivo-cochlear bundle in relation to the outer hair cells of the organ of Corti in guinea pig. *Acta Oto-Laryngologica, Stockholm*, **55**, 11–32.

LISBERGER, G. G. and FUCHS, A. F. (1977) Role of the primate flocculus in smooth pursuit eye movements and rapid behavioural modification of the vestibulo-ocular reflex. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North Holland, pp. 381–389.

LLINÁS, R. and PRECHT, W. (1969) The inhibitory vestibular efferent system and its relation to the cerebellum of the frog. *Experimental Brain Research*, **9**, 16–29.

—— —— and KITAI, S. T. (1967) Cerebellar Purkinje cell projection to the peripheral vestibular organ in the frog. *Science*, **158**, 1328–1330.

MARR, D. (1969) A theory of cerebellar cortex. *Journal of Physiology, London*, **202**, 437–470.

NODA, H., ASOH, R. and SHIBAGAKI, M. (1977) Floccular unit activity associated with eye movements and fixation. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North Holland, pp. 371–380.

RAPHAN, T., COHEN, B. and MATSUO, V. (1977) A velocity-storage mechanism responsible for optokinetic nystagmus, optokinetic after-nystagmus and vestibular nystagmus. In: *Control of Gaze by Brain Stem Neurons*. Edited by R. Baker and A. Berthoz. Amsterdam: Elsevier/North Holland, pp. 37–47.

ROBINSON, D. A. (1975) Oculomotor control signals. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Edited by G. Lennerstrand and P. Bach-y-Rita. Oxford: Pergamon Press, pp. 337-378.

SINGLETON, G. T. (1967) Relationship of the cerebellar nodulus to vestibular function—a study of the effects of nodulectomy on habituation. *Laryngoscope*, **77**, 1579-1620.

STEIN, M. B. and CARPENTER, M. B. (1967) Control projections of portions of the vestibular ganglia innervating specific parts of the labyrinth in the rhesus monkey. *American Journal of Anatomy*, **120**, 281-318.

TAKEMORI, S. and COHEN, B. (1974) Loss of visual suppression of vestibular nystagmus after flocculus lesion. *Brain Research, Amsterdam*, **72**, 213-224.

—— and SUZUKI, M. (1977) Cerebellar contribution to oculomotor function. *ORL; Journal for Oto-Rhino-Laryngology and its Borderlands, Basel*, **39**, 209-217.

—— —— (1978) Cerebellar control of the vestibulo-oculomotor reflex. In: *Vestibular Mechanisms in Health and Disease*. Edited by J. D. Hood. London: Academic Press, pp. 99-106.

TJERNSTRÖM, O. (1973) Nystagmus inhibition as an effect of eye closure. *Acta Oto-Laryngologica, Stockholm*, **75**, 408-418.

TRINDER, E. (1975) Instrument for the on-line measurement of the slow phase of nystagmus. *Aviation, Space and Environmental Medicine*, **46**, 441-444.

WOLFE, J. W. (1968) Evidence for control of nystagmic habituation by folium-tuber vermis and fastigial nuclei. *Acta Oto-Laryngologica, Stockholm*, Supplement **231**, 1-48.

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PLASTICITY IN SPEECH ORGANIZATION FOLLOWING COMMISSUROTOMY

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INTRODUCTION

WE have been studying the cognitive and conscious mechanisms in the separated hemispheres of Case P.S., who at the age of 15 years underwent complete surgical section of the corpus callosum in an effort to manage his otherwise intractable epileptic seizures of longstanding duration (Wilson, Reeves, Gazzaniga and Culver, 1977). Immediately following the operation, P.S., like other split-brain patients, was unable to verbally describe stimuli presented exclusively to his left visual field as these stimuli were directed to his mute right hemisphere (Gazzaniga and Sperry, 1967). He was observed, however, to be capable of behaving as if he comprehended a wide range of language-related stimuli presented to his right hemisphere, although he was completely incapable of describing verbally the nature of the stimuli; he was able to spell by writing with the left hand (Gazzaniga, LeDoux and Wilson, 1977; Gazzaniga and LeDoux, 1978). Now, starting approximately two years post-operatively, P.S. has begun to speak about stimuli exposed in his left visual field.

The development of left visual field naming in the case of P.S. could be attributable to either reinstatement of visual interhemispheric transfer in the visual modality or to the acquisition of speech by the right hemisphere. This report describes the continuing series of experiments that suggest P.S.'s newly acquired capacity may represent the late development of speech in his right hemisphere following callosotomy.

CASE HISTORY AND METHOD

P.S., a right-handed boy, experienced a series of severe convulsions at about 2 years of age, with a seizure focus identified in the left temporal region by electroencephalography. Following this early activity, he apparently developed normally until the age of 10 years when generalized seizures recurred spontaneously and became intractable. In January, 1976, he was operated on for complete surgical section of the corpus callosum. A complete medical history has been published elsewhere (Wilson *et al.*, 1977).

All tasks involved the lateralized presentation of visual stimuli. The subject was seated 1 m from an opaque screen and instructed to fixate on a dot in the centre of the screen. By means of a standard slide projector fitted with an electronic shutter, stimuli were presented at least 5 degrees to the right or left of fixation for 150 ms. Left visual field exposure lateralizes input to the right hemisphere and right field exposure results in left hemisphere lateralization. The stimuli were positive slides of words, pictures, numbers, letters, or nonsense figures not subject to verbal coding, that were rear-projected on to a screen which the subject faced. Further, these stimuli subtended a horizontal visual angle of 2.4 to 3.2 degrees so that the greatest eccentricity from fixation was 8.2 degrees. Because of the line-drawn nature of the picture, word, letter, and number stimuli, measurements of luminosity varied less than 0.5 per cent on all bilaterally simultaneously projected trials. Prior to each exposure, the subject was asked to fixate a point in the midline on the screen. Eye movements were carefully monitored through the use of a video recorder and camera fitted with a 10:1 zoom lens. Tests are carried out once a month in a specially designed mobile testing laboratory.

OBSERVATIONS

Visual Field Naming

The subject was asked to describe identical sets of single three- or four-letter words or single line-drawn pictorial stimuli lateralized to either right or left visual field. Approximately six months post-operatively, he was completely incapable of verbally identifying the nature of left visual field stimuli, but had no problems with right visual field stimuli. One and one-half years post-operatively the results were the same. However, during the recent testing periods twenty-six to thirty-six months

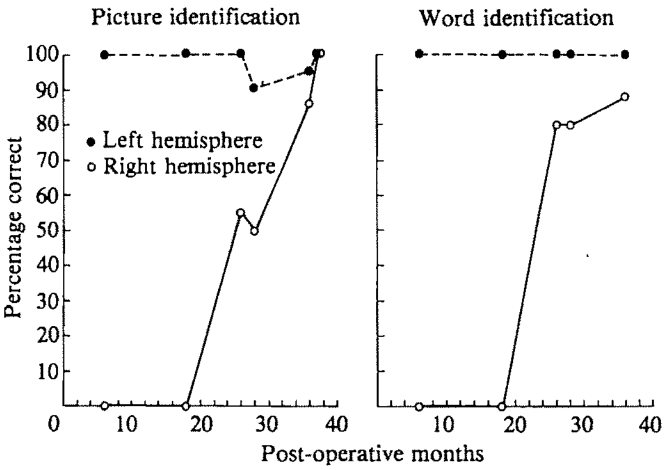

FIG. 1. *Naming of Lateralized Stimuli.* There was a complete inability to name words or pictures in the left visual field during the first eighteen post-operative months. Number of trials ⩾ 25. The developing ability to name left visual field stimuli, beginning some twenty-six months post-operatively, has continued to the present. Number of trials ⩾ 10.

post-operatively (he underwent operation in January, 1976), there has been a marked increase in his capacity to name left visual field stimuli (fig. 1). The predominate error pattern after the first eighteen post-operative months revealed that P.S. almost always insisted he saw nothing or, at best, a 'flash' on the left visual field exposures. When given the opportunity to respond nonverbally, however, he was nearly always correct in pointing to the object which matched the left visual field stimulus (Risse, LeDoux, Springer, Wilson and Gazzaniga, 1978; Gazzaniga *et al.*, 1977).

Same-Different Judgements

The picture and word stimuli used for these trials were the same type as those used for the single field naming. Numbers and single letters were also used. Nonsense figures consisted of amorphous black designs on a white background that were easy to visualize but difficult to name. For these trials P.S. was asked first to state whether two simultaneously presented stimuli were the same or different. When the two stimuli were both presented within either visual field (*see* fig. 2) the same-different judgements were quite accurate. These trials were significantly different from chance ($P < 0.001$), and the decline in accuracy from the initial measurements to the present is more apparent than real. When the judgements required interfield comparisons, however, performance fell to chance ($P = 0.07$), a significant change from the intrafield comparisons (fig. 3).

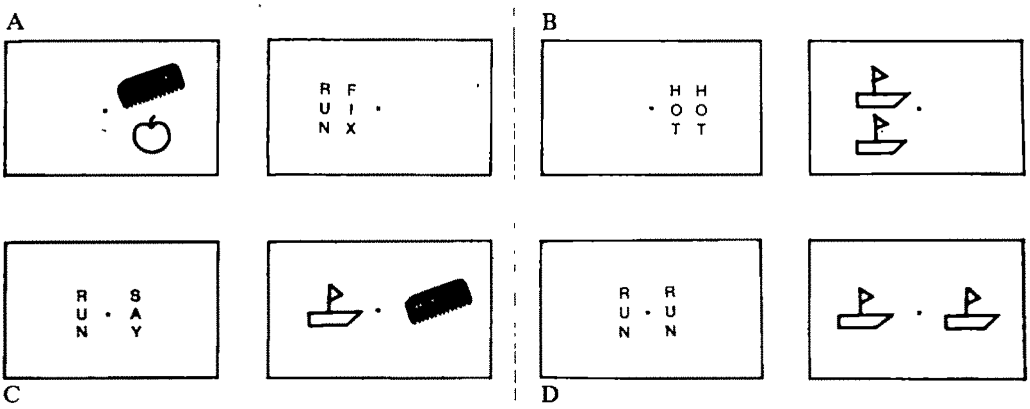

FIG. 2. In A, the word or picture stimuli presented within either right or left field are different. In B, the stimuli are the same. P.S. made accurate judgements in both A and B series of trials. In C and D same-different judgements require interfield comparison and his performance broke down.

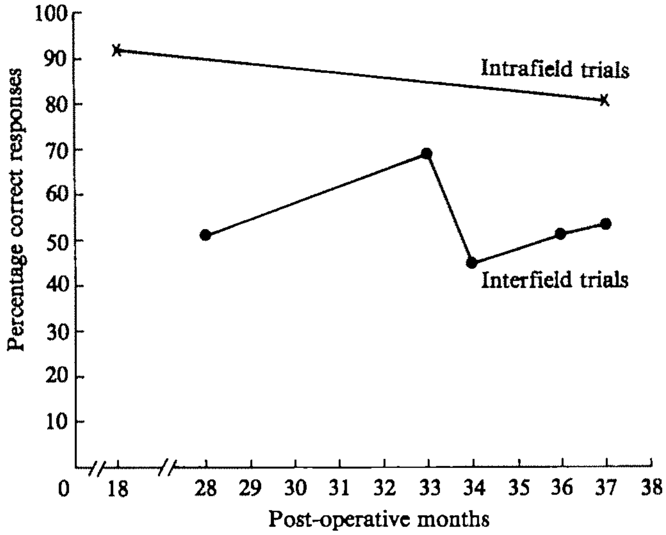

FIG. 3. *Same-Different Judgement.* Intrafield trials (represented by an X) are contrasted with interfield trials (●). Typical examples are shown in fig. 2. Interfield performance is different from chance ($P < 0.001$). Number of trials during each testing session $\geqslant 50$.

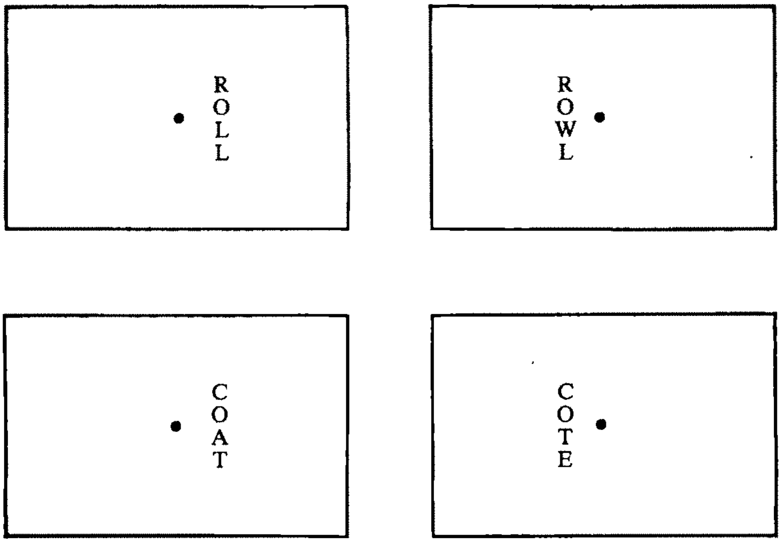

FIG. 4. In these trials P.S. accurately named all stimuli but accurately spelled only the stimuli in the right visual field (left hemisphere). Left visual field stimuli were spelled like the common word of the pair in all instances. *See* Table 1 for results.

TABLE 1. HOMOPHONE TEST

	Left visual field		*Right visual field*	
	Described	*Spelled*	*Described*	*Spelled*
Homophone	7/10	0	7/7	7
Word	13/13	11	14/14	14

Homophone Test

One of a pair of homophones (coat or cote, for example) was presented to one visual field on each trial and P.S. was asked to name what he saw (fig. 4). Subsequent to naming the stimulus, he was asked to spell the word. Following right visual field exposure, the homophones (both members) were correctly named and spelled. Following left visual field exposure, the homophones (both members) were correctly named, but the non-word member of the pair in each instance was spelled incorrectly (*see* Table 1).

Complex Scenes

One of a series of complex pictures was presented to a single visual field on each trial. These scenes portrayed a simple action such as a man holding a gun (*see* fig. 5). Following exposure to either visual field, P.S. produced a single word that accurately characterized that scene. Further, accurate description about the details of the scene occurred only with right visual field/left hemisphere exposure. On left

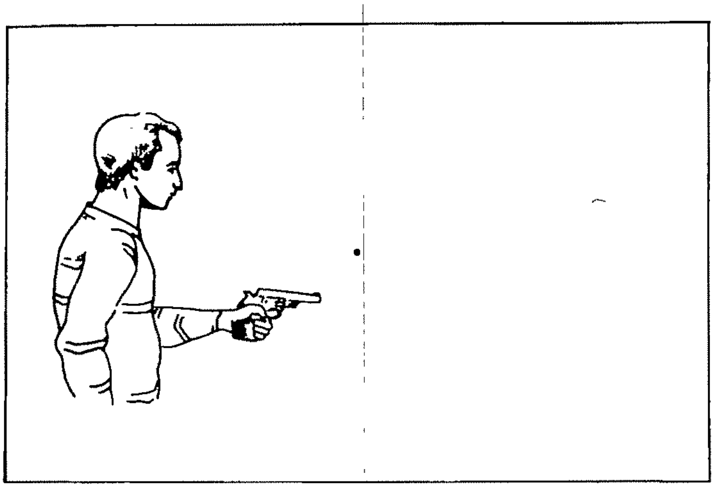

FIG. 5. An example of a complex scene. Pictures like this one were flashed to either the right or the left visual field.

TABLE 2. EXAMPLE OF VERBAL RESPONSE TO COMPLEX PICTURES

Right hemisphere stimulus	*Verbal response*
(A piece of) layer cake	'Cake . . . it was a whole vanilla cake with chocolate icing, silverware is there too'.
Exploding firecracker	'Smoke . . . coming out of a chimney, it's a small house'.
Man, shearing sheep	'Man . . . he is walking through the woods'.
Couple dancing	'Some guys . . . working on building together'.
Man with gun	'Gun . . . hold-up . . . he has a gun and is holding up a bank teller, a counter separates them'.
Left hemisphere stimulus	*Verbal response*
Christmas tree	'A Christmas tree standing alone'.
Fat man, sweating	'Man—big and fat'.
Man with gun	'Guy with a gun'.

visual field exposure, while the word expressed accurately identified the idea represented by the picture, the subsequent explanation, although vivid and detailed, often bore little relation to the content of the picture (*see* Table 2).

Finger Postures

Six line drawings of finger postures were lateralized to each hemisphere (Gazzaniga, 1970). P.S. was required to mimic the postures with each hand. The results in two additional experimental sessions conducted during this twenty-six to thirty-six month post-operative period confirm an earlier report (Gazzaniga *et al.*, 1977) that on right visual field exposure of a finger posture, the right hand assumed the correct posture while the ipsilateral left hand was incorrect on six out of seven trials. This pattern of results was duplicated on left visual field exposure, with the left hand performing the distal co-ordinated act which the right hand could not.

DISCUSSION

Recently, we have described rich language-processing capacities in each hemisphere in the case of P.S. (Gazzaniga *et al.*, 1977; Gazzaniga and LeDoux, 1978). Each hemisphere of this unique young man could process nouns and verbs, as well as rhymes, antonyms, and superordinate concepts when these were presented to either hemisphere by flashing appropriate material in the contralateral visual field. Most striking, however, was the capacity of P.S.'s right hemisphere to produce verbal responses by writing or by the selection and arrangement of letters. This capacity has been contrasted with his left hemisphere's ability to produce normal speech. Now, some two-and-a-half years after complete callosal section, P.S. displays a markedly increased capacity to name verbally left visual field (right hemisphere) stimuli, as well as continued ability to name right visual field (left hemisphere) stimuli.

The mechanism underlying the capacity to name stimuli exposed solely to the left visual field of normal persons who are left hemisphere-dominant for expressive speech typically involves interhemispheric transfer within the visual modality. The left visual field information is projected to the right hemisphere and is then transferred via the commissural system to the left hemisphere where the naming takes place. Surgical section of both the corpus callosum and anterior commissure in man and other primates blocks visual transfer (Gazzaniga, 1965; Black and Myers, 1964). However, when the anterior commissure is spared, visual transfer is typically preserved (Risse *et al.*, 1978; Sullivan and Hamilton, 1973).

Unlike most patients with intact anterior commissures, P.S. was observed to be visually split shortly after section of the callosum, although his anterior commissure was left intact (Risse *et al.*, 1978). Our initial interpretation of the emergence of his capacity to name left visual field stimuli was in terms of the reinstatement of visual transfer. It seemed that his anterior commissure had become functional.

Invoking the visual transfer hypothesis to explain left visual field naming in the case of P.S., however, is not consistent with the above experiments. Callosum-sectioned patients who transfer visual information through the anterior commissure perform like neurologically intact subjects on visual transfer tests requiring inter-field integration. That is, they are capable of stating whether two stimuli, one in each visual field, are the same or different. P.S. was capable of making accurate same-different judgements when the stimuli were both within a single visual field. However, on trials requiring interfield integration where he had to make a judgement about both fields simultaneously, his performance fell to chance. Moreover, inter-field performance was not influenced by the nature of the stimuli involved. He was no better at making interfield judgements involving two pictures, or a word and a picture, than he was when a one-syllable word appeared in each field. These observations show that information channelled to one hemisphere remains inaccessible to the other, and argues against the notion of interhemispheric transfer of visually encoded information.

A further argument against the interhemispheric transfer hypothesis emerged from a test requiring finger movements in response to lateralized visual cues. Each hemisphere has more or less exclusive motor control over the contralateral distal extremities (Gazzaniga, 1970; Gazzaniga and LeDoux, 1978; Brinkman and Kuypers, 1973). Thus, split-brain patients who do not show transfer, when exposed to line drawings of finger postures in one visual field, are unable to mimic the posture with the hand ipsilateral to the exposed hemisphere. Subjects who transfer visual messages between their hemispheres can mimic the postures with either hand following lateralized exposure because the visual cue ultimately reaches both hemispheres. P.S. accurately mimicked postures with the contralateral hand, but performed poorly with the hand ipsilateral to the exposed hemisphere. It appears, then, that visual transfer is not occurring in P.S. through the anterior commissure or any other pathway.

Further exploring the nature of P.S.'s verbal response to left visual field stimuli, several experiments were performed. In the homophone test, when non-words like 'cote' were presented in the left visual field, they were correctly named. Yet, when subsequently asked to spell the stimulus, P.S. spelled the word analogue ('c-o-a-t') of the non-word. If the basis for left field naming was the transfer of the visual stimulus from the right to the left hemisphere, then the hemisphere that said 'cote' should also have spelled 'c-o-t-e'. Both words and non-words were correctly named and spelled following right visual field (left hemisphere) exposure. As in the experiments with single syllable words, inability to perform same or different judgements when the homonym word-pair was simultaneously flashed to both visual fields discredits phonemic transfer to the left hemisphere as the source of left visual field naming.

Over a series of homonym trials the hemisphere that spelled the word (for example, 'c-o-a-t') was not the hemisphere that received the visual input and emitted the output 'cote'. It seems that the right hemisphere when presented with 'cote', emitted the appropriate phoneme. The left hemisphere, which has the more robust and competent speech system, upon receiving the phoneme as an auditory input, assumed control over the situation. Only having access to the auditory properties of the spoken stimulus (kōt, the phonetic description of cote), the left hemisphere produced the spelling of the word counterpart from the flashed non-word.

P.S.'s right hemisphere can now process language in a sophisticated manner. Not only can his right hemisphere emit appropriate writing and spelling, and distinguish nouns, verbs, and superordinate concepts, but it also seems able to vocalize. During each of the many sessions we have observed and video-taped P.S.'s behaviour. The left visual field-right hemisphere trials provoke behaviour that is different from right visual field-left hemisphere speech. In some instances, after left visual field stimulation, an audible response did not occur. However, P.S.'s face, mouth and tongue adopted a posture that appeared appropriate for the verbal expression of the word or picture stimulus. This posturing prior to verbal expression did not occur after right visual field stimulation. Using sensitive equipment we recorded and amplified otherwise inaudible whispers, and actually heard the appropriate word spoken in conjunction with the posturing. More frequently than ever, though, responses to left visual field stimuli are no longer whispers, and, as the results of the present experiments demonstrate, audible and accurate words are produced.

Concerning the mechanism of P.S.'s right hemisphere capabilities, it may be that the language mechanisms of the left hemisphere assume control soon after the right hemisphere programmes the muscles of phonation. For example, when the complex scenes (fig. 5) are projected to the right visual field-left hemisphere, P.S. responds in a rather ordinary fashion. However, on those trials in which the complex scene is projected to the left visual field-right hemisphere, the response pattern is quite different (Table 2). On these left visual field trials he emits a word or two that identifies the dominant activity of the scene but which seems to establish the context for a subsequent, seemingly unrelated, response. These verbal responses bear little relation to the exposed slide, but remain a plausible use of the ejaculated single word response. Furthermore, once he has emitted the initial single word, he tends not to ignore this choice and insists that the subsequent description identified the essence of the exposed slide.

What is of particular interest, of course, is the plain fact that P.S. behaves as if he has absolutely no insight that these story reconstructions of stimuli presented to the right hemisphere are spurious. Through his verbal behaviour, however, he appears very intent on constructing a unity. With an instantaneous response, the left hemisphere moves to construct a theory for a behaviour emitted from the 'self'. This is done by a half-brain that never makes confabulatory responses in test situations which exceed an informational load presented to the left hemisphere. The implications of this for a theory of mind have been expanded elsewhere (Gazzaniga, 1978).

From another aspect, this limited speech capacity of the right hemisphere may reflect an early stage of development for an emerging speech system, even though on physical examination P.S. is clearly an adult. There are only rare clinical reports of language acquisition in late childhood-early adolescence, although there is more evidence regarding the functional recovery of language in groups of childhood aphasics (Hécaen, 1976). Some of the theories have suggested a 'critical period' during which language development depends on necessary neurological events and an unspecified minimal language exposure (Lenneberg, 1967). More molecular, but not completely analogous, non-primate models suggest that sexual hormones may also influence these timing phenomena (Nottebohm, 1977). The emerging speech system in P.S., now that he is beyond any critical period, supports a notion that for a given brain area to become functional, certain cognitive and emotional states must obtain. P.S., unlike all other split-brain patients, was able to respond appropriately to linguistic inputs to the right hemisphere immediately after operation. He was able to respond to verbal questions asked of him by spelling out appropriate answers within the first post-operative year (Gazzaniga *et al.*, 1977), and over two years has been found capable of differently evaluating emotionally rated words (LeDoux, Wilson and Gazzaniga, 1977). In short, although the right hemisphere of P.S. is unique, it represents a developing mental entity that through each of our evaluative measures continues to appear self-aware. It is a mental system of this character that has learned to talk.

The appearance of any linguistic capacity in the right hemisphere of P.S. and other split-brain patients (Gazzaniga, 1970; Zaidel, 1978) is associated with early left hemisphere pathology, and this development does not necessarily reflect normal brain organization. However, acknowledging the early left temporal seizures in this unusual man does not help to explain the progressive development of speech in the right hemisphere, and further experiments will be required to follow and clarify these issues. Yet from another point of view, this study suggests clues underlying the lack of significant recovery in the typical adult patient who is rendered globally aphasic. The loss of language in these patients is so devastating it may be that the remaining cognitive and emotional systems provide little motivation to regain the ability to use language again.

SUMMARY

For three-and-a-half years we have been studying the cognitive and conscious mechanisms in a remarkable 18-year-old man: Case P.S. This unique individual had his corpus callosum divided in order to control intractable epilepsy. Although for some time after the operation he appeared like other split-brain patients, unable to describe verbally stimuli directed to his mute right hemisphere, he behaved as if he was capable of comprehending a wide range of language-related stimuli directed to that hemisphere. Spelling by choosing the appropriate letters with his left hand, he could process nouns, verbs, rhymes, antonyms, and superordinate concepts. When asked about tachistoscopic presentations delivered to his left visual field, he either said he had seen nothing, or only a flash of light. He was also unable to identify verbally tactile 'stereognostic' inputs to his left hand.

In the last year P.S. has begun to speak about stimuli directed to his right hemisphere. This series of experiments suggests that this speech is not interhemispheric transfer within the visual modality. Further, plotting the relative increased proficiency of verbal description of inputs directed to the right hemisphere, this speech system seems to be in a process of continuing development.

REFERENCES

BLACK, P. and MYERS, R. E. (1964) Visual functions of the forebrain commissures in the chimpanzee. *Science*, **146**, 799-800.

BRINKMAN, S. and KUYPERS, H. G. J. M. (1973) Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. *Brain*, **96**, 653-674.

GAZZANIGA, M. S. (1965) Interhemispheric communications of visual learning. *Neuropsychologia*, **4**, 183-189.

—— (1970) *The Bisected Brain.* New York: Appleton Century Crofts.

—— (1978) On dividing the self: Speculations from brain research. In: *Neurology. Proceedings of the 11th World Congress of Neurology, Amsterdam, September 11-16, 1977.* Edited by W. A. den Hartog Jager, G. W. Bruyn and A. P. J. Heijstee. International Congress Series No. 434. Amsterdam: Excerpta Medica, pp. 233-44.

—— and HILLYARD, S. A. (1971) Language and speech capacity of the right hemisphere. *Neuropsychologia*, **9**, 273-280.

—— and LEDOUX, J. E. (1978) *The Integrated Mind.* New York: Plenum Press.

—— · —— and WILSON, D. H. (1977) Language, praxis, and the right hemisphere: clues to some mechanisms of consciousness. *Neurology, Minneapolis*, **27**, 1144-47.

—— and SPERRY, R. W. (1967) Language after section of the cerebral commissures. *Brain*, **90**, 131-138.

HÉCAEN, H. (1976) Acquired aphasia in children and the ontogenesis of hemispheric functional specialization. *Brain and Language*, **3**, 114-134.

LEDOUX, J. E., WILSON, D. H. and GAZZANIGA, M. S. (1977) A divided mind: observations on the conscious properties of the separated hemispheres. *Annals of Neurology*, **2**, 417–421.

LENNEBERG, E. H. (1967) *The Biological Foundations of Language*. New York: J. Wiley.

NOTTEBOHM, F. (1977) Origins and mechanisms in the establishment of cerebral dominance. In: *Handbook of Behavioral Neurobiology*. Edited by M. S. Gazzaniga. New York: Plenum Press.

RISSE, G. L., LEDOUX, J. E., SPRINGER, S. P., WILSON, D. H. and GAZZANIGA, M. S. (1978) The anterior commissure in man: Functional variation in a multisensory system. *Neuropsychologia*, **16**, 23–34.

SULLIVAN, M. V. and HAMILTON, C. R. (1973) Interocular transfer of reversed and non-reversed discrimination via the anterior commissure in monkeys. *Physiological Behavior*, **10**, 355–359.

WILSON, D. H., REEVES, A. G., GAZZANIGA, M. S. and CULVER, C. (1977) Cerebral commissurotomy for the control of intractable seizures. *Neurology, Minneapolis*, **27**, 708–715.

ZAIDEL, E. (1978) Auditory language comprehension in the right hemisphere following cerebral commissurotomy and hemispherectomy: a comparison with child language and aphasia. In: *Language Acquisition and Language Breakdown: Parallels and Divergencies*. Edited by A. Caramazza and E. B. Zurif. Baltimore: Johns Hopkins Press, pp. 229–275.

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QUANTITATIVE STUDIES OF SACCADIC AND PURSUIT EYE MOVEMENTS IN MULTIPLE SCLEROSIS[1]

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INTRODUCTION

THERE have been few quantitative studies of ocular kinetics in patients with multiple sclerosis. Slowing of saccade velocities has been found in patients with internuclear ophthalmoplegia (Baloh, Konrad, Sills and Honrubia, 1975; Bird and Leech, 1976; Mastaglia, Black and Collins, 1976*a*) and also in some patients without clinical abnormalities of eye movements (Mastaglia *et al.*, 1976*a*). Abnormalities of saccade reaction time and accuracy (Solingen, Baloh, Myers and Ellison, 1977; Ochs, Hoyt, Stark and Patchman, 1978) and of pursuit movements have also been reported in some multiple sclerosis subjects (Solingen *et al.*, 1977). However, there has been no systematic study of the contribution of such studies to the evaluation of ocular movements in patients with multiple sclerosis, and in particular to the detection of subclinical involvement of the ocular motor pathways in patients with suspected multiple sclerosis.

We report our findings in 108 patients with established or suspected multiple sclerosis in whom quantitative electro-oculography was carried out using an on-line computerized technique. The contribution of the finding of subclinical abnormalities of horizontal eye movement has been evaluated in those patients in whom the diagnosis was not clinically definite, and has been compared to that of pattern-reversal visual evoked potentials (VEP) (Halliday, McDonald and Mushin, 1973; Mastaglia *et al.*, 1976*b*; Mastaglia, Black, Cala and Collins, 1977; Collins, Black and Mastaglia, 1978) which were also recorded in all patients.

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MATERIALS AND METHODS

Patients

The subjects comprised 82 females and 26 males, 19 to 64 years of age (mean age 39 years), and were classified into the *clinically definite*, *early probable or latent*, *suspected* and *progressive probable* multiple sclerosis categories suggested by McDonald and Halliday (1977) on the basis of clinical criteria and the results of visual and somatosensory evoked potential studies (Mastaglia *et al.*, 1976*b*, *c*, 1977). The first group comprised 39 patients with a remitting and relapsing history of two or more episodes of neurological dysfunction and with clinical and/or electrophysiological evidence of lesions at two or more sites in the central nervous system. The *early probable or latent* group comprised 15 patients with a history of a single episode of demyelination but with clinical and/or electrophysiological evidence of two or more separate lesions, or with only a single lesion compatible with multiple sclerosis but with a remitting and relapsing course. The 50 patients in the *suspected* multiple sclerosis group had presented with an initial episode suggestive of multiple sclerosis with clinical and/or electrophysiological evidence of only a single lesion, or had equivocal clinical findings at the time of examination. The 4 patients in the last group had non-familial, asymmetric progressive syndromes with spinal cord, cerebellar or visual involvement. The time since onset of symptoms was one to thirty years in the *clinically definite* group, one month to twenty-five years in the *early probable or latent* group, one month to twelve years in the *suspected* group and two to twenty-five years in the *progressive probable* group. Patients taking anticonvulsants or other drugs known to affect the ocular motor system were not included in the study.

Electro-oculography

Electro-oculograms (EOG) were recorded differentially from each eye using two pairs of Grass disc electrodes applied close to the inner and outer canthi. Details of the data collection and computer analysis procedures have been presented in full elsewhere (Black, Mastaglia and Collins, 1978). Two different techniques were used for eliciting eye movements and for analysis of the EOG.

(1) *Refixation saccades.* The subject was seated 310 cm from a screen on which were mounted two small red light sources which subtended an angle of 25 degrees at the eye. Saccades were generated by the patient alternately refixating between the two light sources at a rate of one or two per second in time with a prompting loud-speaker click. The EOG signals were passed to modified Devices 3160 differential preamplifiers with gains set to 1,000 and low and high frequency roll-off settings of 0.016 Hz and 35 Hz. The analogue data were then passed to variable gain purpose-designed DC amplifiers prior to analogue-to-digital conversion and analysis by a PDP 11/40 computer. The analysis programme allowed peak velocities to be extracted separately for abducting and adducting movements of each eye. The peak velocity was measured over a 24 ms period at the midpoint of the excursion of the eye. Mean adducting and abducting velocities and the ratio between abducting and adducting velocities for each eye were provided at the end of five 12.28 s measurement periods. Sixty-two patients were studied using this technique. Normal ranges were established in 21 normal volunteers 21 to 51 years of age who were not taking drugs and who had no detectable abnormality of eye movement (Table 1).

(2) *Moving spot technique.* The patient was seated 155 cm from a screen on to which a light spot was projected from a projector-galvanometer-mirror system mounted above and behind the patient approximately 3.8 m from the screen. The direction and velocity of movement of the light spot was controlled directly by the computer through a digital-to-analogue channel.

Saccadic movements. The spot was made to jump at high velocity ($\sim$ 1500 deg s^{-1}) in the horizontal plane through an angle of 15 degrees from fixation, each test involving 25 'jumps', 12 to the left, followed by 13 to the right. The EOG signals were dealt with in the same way as in the first technique but were electronically differentiated prior to analogue-to-digital conversion. The instantaneous eye movement velocity was derived by the computer program from the differentiated wave-form and not from the amplified EOG voltages as in the first technique. The analysis programme allowed the following parameters to be extracted separately from abducting and adducting movements of each eye: saccade reaction time (ms); peak eye movement velocity (deg s^{-1}); saccade accuracy expressed as the percentage ratio of first saccade amplitude to target movement amplitude. Normal ranges for these parameters were established from the means ±2 SD in 24 healthy volunteers 12 to 50 years of age, who were not on drugs, and who had no apparent abnormality of eye movement on clinical testing (Table 1). As shown in figs. 2 and 3, in 2 of the normal subjects saccade reaction time and/or accuracy values fell outside the established normal ranges suggesting that a mild subclinical abnormality was present in these individuals. This finding is in accord with the experience of Gresty (1977) who found unexpected saccade abnormalities in 4 out of 15 'normal' subjects.

Pursuit movements. The spot was made to move in the horizontal plane at a number of constant velocities in the range from 10 to 70 deg s^{-1}, the velocity for any particular sweep being chosen using the computer software random number generator. Any given study always included the velocities 10, 20, 30, 40 and 50 deg s^{-1} interspersed among other randomly chosen velocities. The direction of movement was also random. Each study comprised 50 movements of the spot, approximately half of them in each direction. It was found that in normal subjects tracking at all velocities over 10 deg s^{-1} was a composite movement of low velocity smooth pursuit and interposed high velocity microsaccades, the latter accounting for an increasing proportion of the 15 degree angle traversed at the higher target velocities (*see* fig. 4).

For target movements of 20 and 40 deg s^{-1} the analysis programme allowed the following parameters to be extracted: the latency, velocity, amplitude and accuracy of the first saccade; the first-to-second inter-saccade interval; the velocity between the first and second saccades; and the average eye velocity throughout the movement. In addition, the relationship between the average eye velocity and target velocity was determined for all target velocities and was displayed graphically.

The studies of saccadic eye movements were performed in 60 patients and the pursuit studies in 42 of these. Seventeen of these 60 patients had previously been studied by the refixation technique for saccadic movements.

In addition to the quantitative analyses, the EOG waveform displayed graphically during the calibration routine at the beginning of each study was analysed visually for obvious abnormalities.

The full analysis of saccadic and pursuit movements was completed in approximately twenty minutes and problems were not encountered with subject fatigue. The head was not rigidly fixed during the procedure but a posterior head support was provided and the subject was given detailed instructions beforehand and urged not to move the head. The occasional patient who found it impossible to maintain a fixed head position was excluded from the study.

TABLE 1. ESTABLISHED NORMAL RANGES (MEANS ±2 SD) FOR SACCADE PARAMETERS*

	Abduction	*Adduction*
Saccade Velocity** (21 subjects)†	272–488 deg s^{-1}	295–545 deg s^{-1}
Full saccade analysis (24 subjects)‡		
Reaction time	154–303 ms	156–295 ms
Peak velocity**	270–358 deg s^{-1}	304–397 deg s^{-1}
Accuracy	93–104%	97–107%

* Mean values for abduction and adduction were calculated for each subject and were then averaged for each of the two groups of normal subjects. ** Values for saccade velocities are lower than those reported by previous workers (see Bird and Leech, 1976). This is due largely to the 'smoothing' routines used in the early part of the EOG analysis programmes (Black, *et al.*, 1978). † 21 to 51 years of age (mean age 40 years). ‡ 12 to 50 years of age (mean age 37 years).

RESULTS

Saccade Velocities

The findings in patients in whom saccade velocities alone were measured are summarized in Table 2. Abnormalities were found in 17 out of 29 (58 per cent) patients in the *clinically definite* group, including 7 with clinically normal eye movements. In the *early probable or latent* and *suspected* groups, abnormalities were found in 10 out of 33 patients (30 per cent) and were subclinical in 4 of these. Abnormalities additional to those noted clinically were found in 3 patients in the *clinically definite* and in one patient in the *suspected* category.

The patterns of abnormality found are summarized in Table 3. Slowing of ocular adduction alone suggesting an internuclear ophthalmoplegia was present in 7 cases, being unilateral in 4 and bilateral in 3. In 2 cases the unilateral adduction paresis was not apparent on clinical examination, while in one case thought to have only unilateral adduction paresis clinically, adducting velocities were reduced bilaterally by up to 87 per cent and there was additional bilateral slowing of abducting velocities which were reduced by up to 60 per cent. Normal velocities were found in 2 patients who when seen five and seven months previously had a bilateral internuclear ophthalmoplegia which had subsequently resolved. In 5 patients from the *clinically definite* and *early probable or latent* groups, all of whom were considered to have normal eye movements clinically, isolated unilateral slowing of abducting velocities, indicating sixth nerve dysfunction, was found. In 3 patients, 2 of whom had normal eye movements clinically, ipsilateral monocular slowing of both adducting and abducting velocities was found, suggesting an ipsilateral pontine tegmental lesion involving both the medial longitudinal fasciculus and the sixth nerve complex. One patient had unilateral slowing of abducting and contralateral slowing of adducting velocities, indicating a subclinical conjugate gaze paresis, while in 4 patients all velocities were reduced to about the same extent suggesting bilateral involvement of supranuclear pathways.

TABLE 2. INCIDENCE OF NORMAL FINDINGS AND OF ABNORMALITIES IN THE 62 MULTIPLE SCLEROSIS PATIENTS IN WHOM SACCADE VELOCITIES ALONE WERE MEASURED

Clinical category	*Normal*	*Abnormal*	*Subclinical* abnormality*
Clinically definite (29)	12	17 (58%)	7 (24%)
Early probable or latent (9)	5	4 (44%)	1 (11%)
Suspected (24)	18	6 (25%)	3 (13%)
Total	35 (56%)	27 (44%)	11 (18%)

* No abnormality of eye movements detected on clinical examination.

TABLE 3. ABNORMALITIES FOUND IN 105 PATIENTS WHO HAD THE SACCADE VELOCITY TEST AND/OR FULL SACCADE ANALYSIS**

	Saccade velocity test	*Full saccade analysis*			
		SRT	*SV*	*SA*	*SRT/SV/SA****
Adduction paresis					
Unilateral	4	2	0	2	4
Bilateral	3	0	2*	2*	3
Adduction paresis with less severe abduction paresis	4	6	9	9	10
Abduction paresis					
Unilateral	5	0	1*	2*	2
Bilateral	0	0	1*	1*	1
Ipsilateral adduction and abduction paresis	3	0	0	0	0
Conjugate gaze paresis	1	7*	0	1*	7
Global saccadic paresis	4	6	2*	1*	7

* Signifies patients with abnormalities of more than one parameter. ** 17 patients had both types of study. *** Abnormality of one or more of these parameters. SRT = saccade reaction time. SV = saccade velocity. SA = saccade accuracy.

Full Saccade Analysis

The findings in the 60 patients in whom the full analysis of saccadic movements was carried out are summarized in Tables 4–6. Abnormalities of one or more of the three saccade parameters measured were found in 34 of the 60 patients, in 22 of whom the clinical examination of eye movements was entirely normal or showed minor abnormalities of dubious significance, for example, mild irregularity or slowing of volitional or following movements. Abnormalities were found in approximately the same proportion of patients in the *clinically definite* group (57 per cent) as in those in the other categories (56 per cent), but were more often subclinical in the latter categories (Table 4).

TABLE 4. INCIDENCE OF ABNORMALITIES OF THE SACCADE REACTION TIME (SRT), SACCADE VELOCITY (SV) AND SACCADE ACCURACY (SA) IN THE 60 MULTIPLE SCLEROSIS PATIENTS WHO HAD THE FULL ANALYSIS OF SACCADIC EYE MOVEMENTS

Clinical category	*SRT*	*SV*	*SA*	*SRT/SV/SA**	*Subclinical abnormalities*
Clinically definite (21)	7	8	8	12 (57%)	6 (29%)
Early probable or latent (6)	1	2	1	2 (33%)	1 (17%)
Suspected (29)	10	7	10	17 (59%)	12 (41%)
Progressive probable (4)	3	0	1	3 (75%)	3 (75%)
Total	21 (35%)	17 (28%)	30 (33%)	34 (57%)	22 (37%)

* Numbers of patients with an abnormality of one or more of the three saccade parameters. For abbreviations *see* Table 3.

While in most patients with clinically abnormal eye movements, and particularly those in the *clinically definite* group, all 3 saccade parameters were usually abnormal, in a significant number of cases with subclinical abnormalities only one or two parameters were abnormal. For example, in some cases saccade reaction times were prolonged while velocities and accuracies were within normal limits (Table 5). The normal range for saccade reaction time was established in 20 healthy volunteers aged up to 50 years (Table 1). Fifteen of the 60 patients with multiple sclerosis in whom measurements of reaction time were made were over this age (52 to 64 years). Of these 15 patients, 11 had reaction times which fell well within the established normal range (< 303 ms for ocular abduction; < 295 ms for ocular adduction). Mean reaction times in the remaining 4 were 325, 350, 340 and 385 ms. In other cases only one or more of the saccade velocities or saccade accuracy measurements were abnormal. When the three saccade parameters were considered individually in patients without clinical abnormalities of eye movement, reaction times and accuracies proved to be more sensitive than velocities in detecting abnormalities. However the highest yield of abnormalities was found when all three parameters were considered (Tables 4 and 5). Thus while saccade velocities were abnormal in only 20 per cent of these cases, when reaction times and accuracies were also taken into consideration, abnormalities were found to be present in 48 per cent of these cases (Table 5).

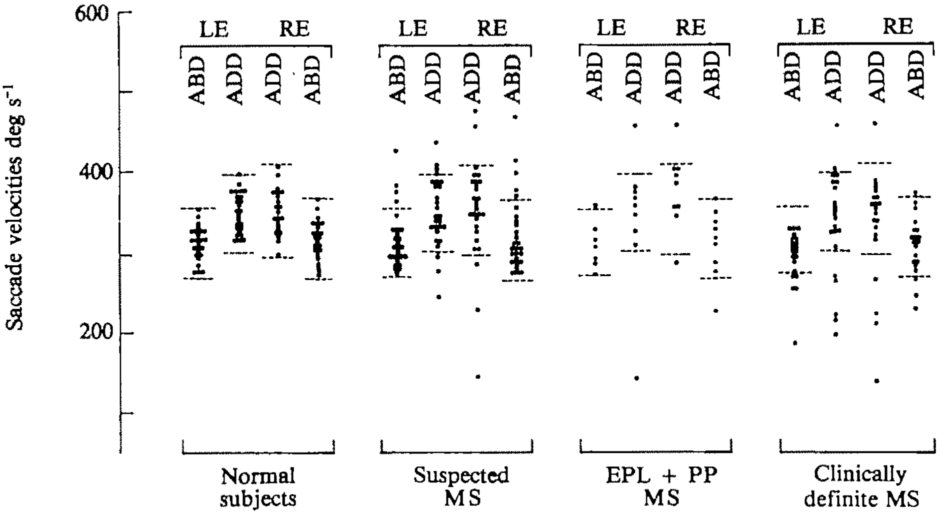


FIG. 1. Distribution of saccade velocities (deg s^{-1}) in normal subjects and in patients with ***suspected, early probable or latent*** (EPL), ***progressive probable*** (PP), and ***clinically definite*** multiple sclerosis (MS). Abducting (ABD) and adducting (ADD) velocities are plotted separately for left and right eyes (LE, RE), each point representing a single subject. The limits of normality (means ±2 SD) are indicated by the interrupted lines.

The magnitude of the changes in saccade reaction time, velocity and accuracy in individual patients in the various categories of multiple sclerosis studied are shown in figs. 1-3, and the patterns of abnormality found in Table 3. As in the case of the

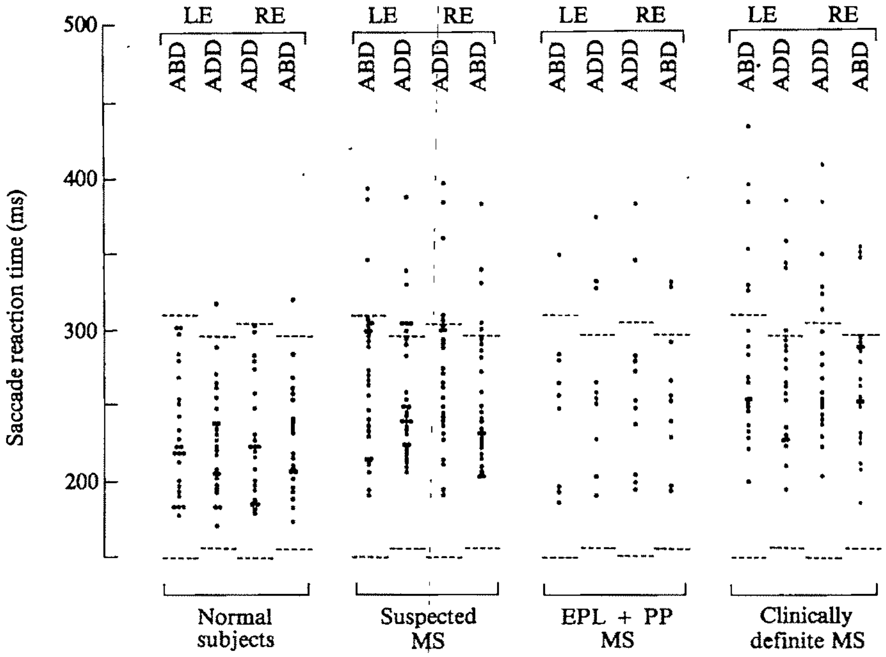


FIG. 2. Saccade reaction times (ms) in normal subjects and in patients with *suspected, early probable or latent* (EPL), *progressive probable* (PP), and *clinically definite* multiple sclerosis. Reaction times are shown separately for abducting (ABD) and adducting (ADD) movements of the two eyes (LE, RE), each point representing a single subject. The limits of normality (means ±2 SD) are indicated by the interrupted lines.

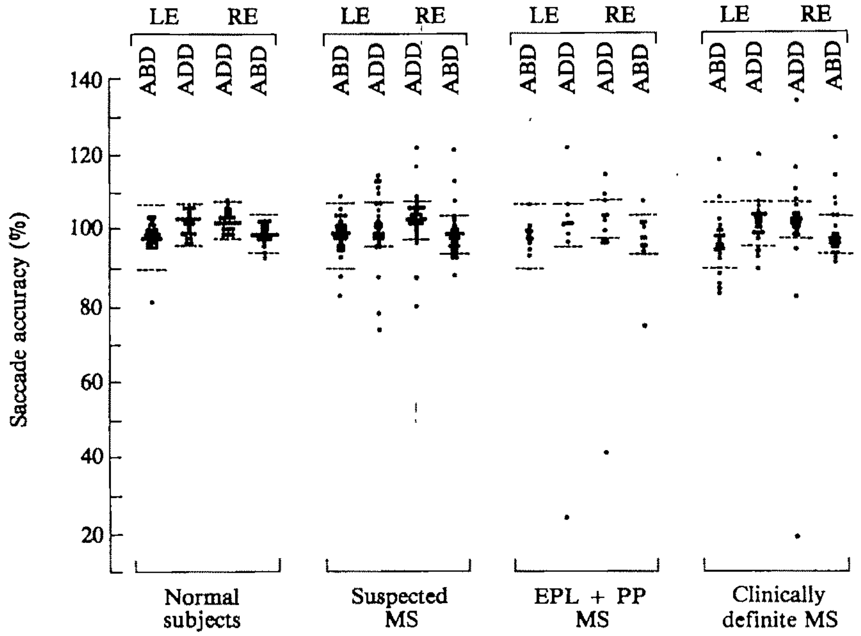


FIG. 3. Saccade accuracies (*see text*) in normal subjects and in patients with *suspected, early probable or latent* (EPL), *progressive probable* (PP), and *clinically definite* multiple sclerosis. Accuracies for abducting (ABD) and adducting (ADD) movements of the two eyes (LE, RE) are plotted separately, each point representing a single subject. The normal limits (means ±2 SD) are indicated by the interrupted lines.

saccade velocity tests, bilateral slowing of ocular adduction was found in some patients with unilateral adduction paresis, and unilateral or bilateral subclinical slowing of ocular abduction was commonly also present in patients with adduction paresis. Subclinical conjugate gaze paresis and global saccadic paresis were found in a total of 14 cases, usually on the basis of saccade reaction times which were prolonged by up to 30 per cent in some cases. Isolated abduction paresis was again an uncommon finding.

Seventeen patients in whom the saccade velocity test was first carried out were subsequently studied by the full saccade analysis technique after intervals of up to six months. In 6 of these an abnormality was shown by both techniques, while in 5 both techniques gave normal results. In 4 patients with normal findings or with a borderline abnormality at the first examination, a definite abnormality was found at the time of the second. In one patient who was found to have a unilateral abduction paresis, and in one who was found to have a unilateral adduction paresis at the first examination, no abnormality was found when the full saccade analysis was subsequently performed.

TABLE 5. INCIDENCE OF ABNORMALITIES OF SACCADE PARAMETERS AND OF PURSUIT MOVEMENTS IN 46 PATIENTS WITH MULTIPLE SCLEROSIS WITH CLINICALLY NORMAL EYE MOVEMENTS

Clinical category	*SRT*	*SV*	*SA*	*SRT/SV/SA**	*Pursuit*	*Saccadic/pursuit***
Clinically definite (13)	3	4	4	6	6/10	9 (69%)
Early probable or latent (5)	0	1	0	1	3/5	3 (60%)
Suspected (24)	9	4	6	12	8/13	15 (63%)
Progressive probable (4)	3	0	1	3	2/3	4 (100%)
Total	15/46 (33%)	9/46 (20%)	11/46 (24%)	22/46 (48%)	19/31 (61%)	31/46 (67%)

* Number of patients with an abnormality of one or more of the saccade parameters. ** Numbers of patients with an abnormality of saccadic and/or pursuit movements. For abbreviations *see* Table 3.

Pursuit Movements

The findings in the 42 patients in whom pursuit movements were also studied are summarized in Tables 5 and 6. Abnormalities were found in 30 (71 per cent) of these patients and were present in a high proportion of patients in each of the clinical categories. Of the 42 patients, all but 2 of those with abnormal saccadic movements also had abnormal pursuit movements. On the other hand, in 9 patients in whom the saccade analysis failed to show any abnormality, pursuit movements were abnormal. Consequently, the overall yield of abnormalities was higher when the results of both the saccadic and pursuit studies were taken into account.

TABLE 6. INCIDENCE OF NORMAL FINDINGS AND OF ABNORMALITIES IN THE 60 PATIENTS WITH MULTIPLE SCLEROSIS WHO HAD THE FULL ANALYSIS OF SACCADIC MOVEMENTS AND IN THE 42 IN WHOM PURSUIT MOVEMENTS WERE ALSO ANALYSED

Clinical category	*Normal*	*Abnormal*			
		Saccadic abnormality	*Pursuit abnormality*	*Saccadic and/or pursuit*	*Subclinical abnormality*
Clinically definite (21)	5	12	14/18	16/21	8
Early probable or latent (6)	2	2	3/4	4/6	3
Suspected (29)	10	17	11/17	19/29	15
Progressive probable (4)	0	3	2/3	4/4	4
Total	17/60 (28%)	34/60 (57%)	30/42 (71%)	43/60 (72%)	30/60 (50%)

Of the 30 patients in whom the pursuit study showed an abnormality, ocular movements had been considered to be normal on clinical examination in 18, and in 7 of these the saccade analysis had also been completely normal. In a number of patients in whom eye movements were normal apart from being excessively jerky ('cogwheeling'), or apart from the presence of nystagmus, the pursuit study was abnormal.

Abnormalities of the pursuit study were detected from examination of the numerical computer print-out, of the tracings of instantaneous adducting and abducting eye movement velocities, and of the plots of eye velocity versus target velocity obtained at the end of the study. Abnormalities were recognized as deviations from the composite pattern of smooth pursuit and interposed microsaccades found in normal subjects (figs. 4–7); as loss of the approximately linear relationship between eye and target velocity for velocities below 40 to 50 deg s^{-1} (fig. 8); or as deviations from the normal in the latency, velocity or amplitude of the first interposed saccade at target velocities of 20 and 40 deg s^{-1}.

Various patterns of abnormality were found. In some patients with adduction or abduction paresis abnormalities were present only when the affected eye moved in the direction of the paresis (fig. 5), whereas in others the abnormalities found were less selective (fig. 6). In some patients in whom following eye movements were considered to be normal or to show only equivocal abnormalities when assessed clinically, the normal relationship between smooth pursuit and interposed saccades was lost, especially at the faster target velocities (fig. 6). Patients with 'cogwheeling' showed an accentuated pattern of interposed saccades both in terms of numbers and amplitude, a greater than normal proportion of the total eye movement being saccadic in nature at all target velocities (fig. 7).

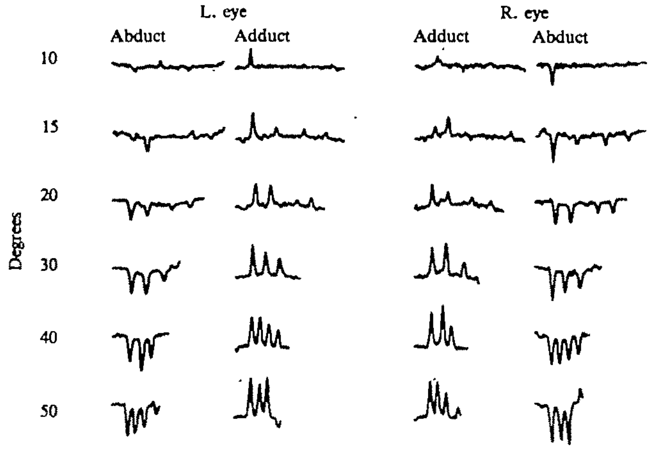


FIG. 4. Computer-derived traces of eye movement velocity (vertical axis) against time (horizontal axis) during tracking of a light spot, moving at constant velocity, through an angle of 15 degrees in the horizontal plane in a 32-year-old normal female. The velocities of spot movement are shown on the left (10, 15, 20, 30, 40 and 50 deg s^{-1}). Left and right eye abduction and adduction velocities are displayed separately. It will be seen that the velocity of eye movement throughout the 15 degrees excursion is not constant, but that at all target velocities periods of low velocity (the relatively flat portion of the trace) are interrupted by a number of high-velocity peaks (the 'spikes' on the traces) which account for an increasing proportion of the angle traversed at the higher target velocities. The actual velocities corresponding to these peaks were of the order of 100 to 250 deg s^{-1} (the velocity being higher at higher target velocities) and they are therefore considered to represent microsaccades which are beyond direct visual resolution.

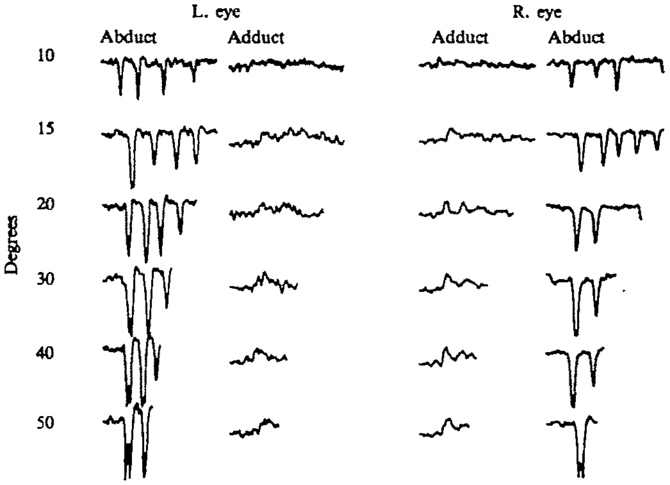


FIG. 5. Horizontal pursuit study (*see* fig. 4) in a 35-year-old female with *suspected* multiple sclerosis with a bilateral internuclear ophthalmoplegia. There is marked impairment of the saccadic component of the movement during ocular adduction. By contrast, interposed microsaccades are more prominent than normal during ocular abduction at the lower target velocities.

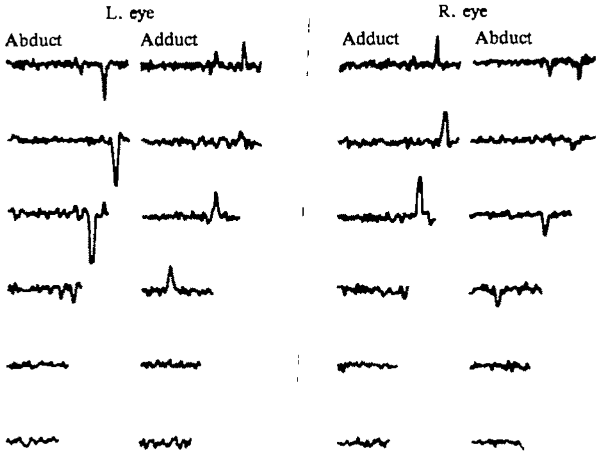


FIG. 6. Horizontal pursuit study in a 44-year-old male from the *suspected* multiple sclerosis group with a spinal cord syndrome and an equivocal abnormality of following eye movements on clinical examination. The normal pattern of interposed microsaccades with increasing target velocities has been lost. The saccadic eye movement study in this patient showed normal saccade velocities but abnormal reaction times and accuracies for left abducting and right adducting saccades.

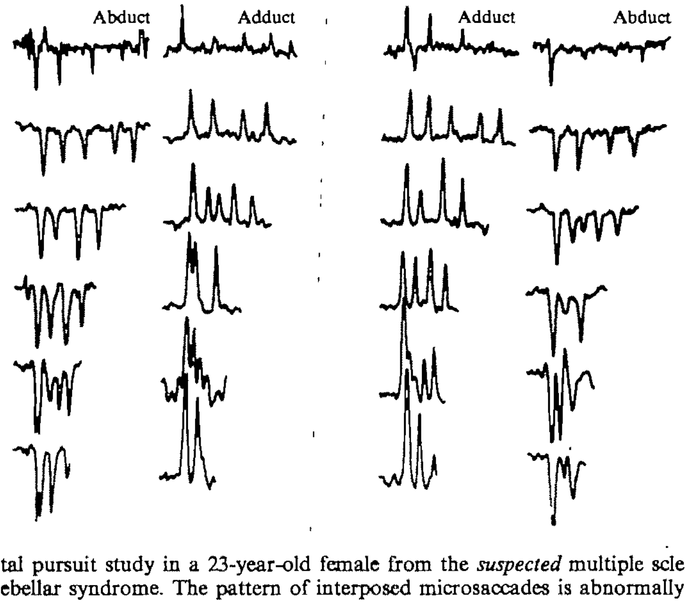


FIG. 7. Horizontal pursuit study in a 23-year-old female from the *suspected* multiple sclerosis group with a predominantly cerebellar syndrome. The pattern of interposed microsaccades is abnormally accentuated at all target velocities.

Reclassification of Patients

The classification of patients in the *early probable or latent* and *suspected* multiple sclerosis categories who presented with spinal cord syndromes was reassessed on the basis of the results of the eye movement studies. The finding of a subclinical abnormality of saccadic and/or pursuit movements allowed reclassification of 2 patients from the *early probable or latent* to the *clinically definite* category and of 12 patients from the *suspected* to the *early probable or latent* category.

Visual Evoked Potentials

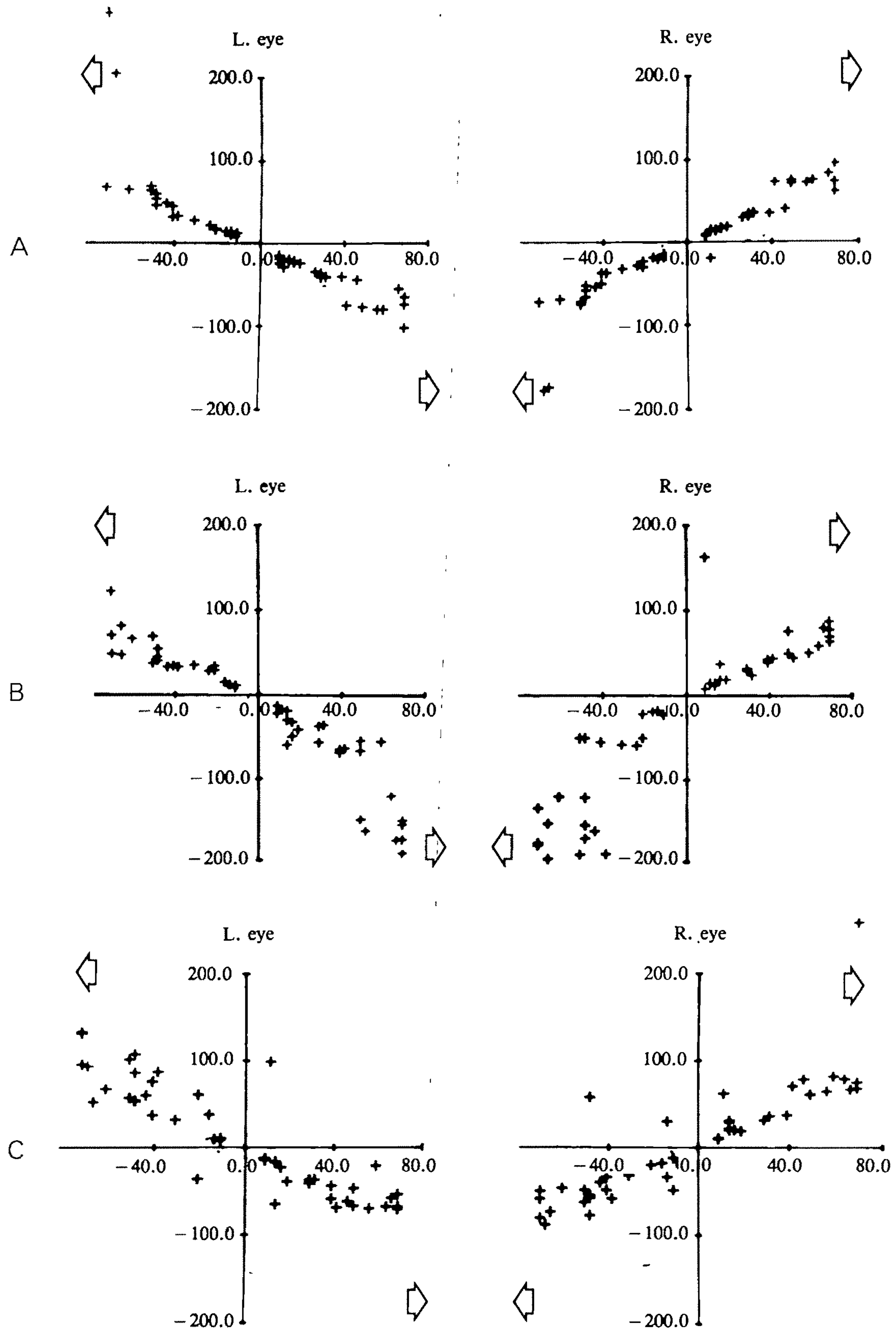
The frequency of abnormalities of the VEP in the patients who had eye movement studies is shown in Table 7. The finding of a subclinical abnormality of the VEP was the basis for the inclusion of 10 patients in the *clinically definite* category and of 9 patients in the *early probable or latent* category. As shown in Table 7 the eye movement studies showed an abnormality in a significant number of patients with normal VEPs, and were normal in only a relatively small number of patients in whom the VEP showed a subclinical abnormality.

TABLE 7. COMPARATIVE INCIDENCE OF ABNORMALITIES OF VISUAL EVOKED POTENTIAL AND OF QUANTITATIVE ELECTRO-OCULOGRAPHIC STUDIES IN PATIENTS IN THE 4 CATEGORIES OF MULTIPLE SCLEROSIS

	Visual evoked potentials		*Electro-oculogram*	
Clinical category	*No. abnormal*	*No. subclinical*	*No. abnormal*†	*No. subclinical*
Clinically definite (39)	30 (77%)	10 (6)*	25 (64%)	11 (6)**
Early probable or latent (15)	4 (27%)	4 (2)	6 (40%)	4 (2)
Suspected (50)	5 (10%)	2 (1)	25 (50%)	15 (14)
Progressive probable (4)	3	1 (0)	4	4 (1)
Total	42/108 (39%)	17 (9)	60/108 (56%)	34 (23)

† Number of patients who showed an abnormality with saccade velocity test or with full saccade analysis, and/or with pursuit movement analysis. * Numbers in brackets refer to the number of patients with normal eye movement studies. ** Numbers in brackets refer to the number of patients with normal VEPs.

FIG. 8. A, *Normal subject.* Plots of average eye movement velocity (deg s^{-1}) on the vertical axis against target movement velocity (deg s^{-1}) on the horizontal axis during horizontal pursuit. An approximately linear relationship is seen for target velocities of up to 40 deg s^{-1} but is not maintained at faster velocities. The direction of eye movement is indicated by the arrows. B, Loss of the normal linear relationship between eye and target velocities during adduction of both eyes in a patient with bilateral internuclear ophthalmoplegia (same case as in fig. 5). C, Loss of the normal relationship between eye and target velocity during abduction and adduction of both eyes in a 34-year-old female with relapsing spastic paraparesis and clinically normal eye movements. The saccade study in this patient showed normal reaction times, velocities and accuracies.


A
L. eye
R. eye
200.0
100.0
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−200.0
−40.0
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B
L. eye
R. eye
200.0
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−200.0
−40.0
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200.0
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80.0

DISCUSSION

The present findings indicate the value of quantitative electro-oculography in the assessment of the functional status of the ocular motor pathways in patients with multiple sclerosis. A high incidence of abnormalities was found not only in those patients with clinically apparent abnormalities of eye movement but also in some in whom the clinical examination showed either no abnormality or minor changes of an equivocal nature. Such subclinical abnormalities were found in 30 per cent of patients in whom the diagnosis was not clinically definite, including 33 per cent of patients in the *suspected* multiple sclerosis category. Patients classified in this latter category were those who had had only a single episode of neurological dysfunction and who had evidence of a lesion at only a single site in the CNS. The finding of a subclinical abnormality of eye movement in such patients is therefore of particular importance as it may provide evidence of an additional lesion in the CNS and thereby increase the degree of diagnostic certainty. As in the case of the pattern-reversal VEP, such a finding was most valuable in patients presenting with isolated spinal cord syndromes and allowed reclassification of a significant number of such patients from the *suspected* to the *early probable or latent* category.

The patterns of ophthalmoplegia found were comparable to those observed clinically. The most frequent consisted of slowing of ocular adduction, reflecting the frequency with which the medial longitudinal fasciculus is involved in multiple sclerosis. In keeping with clinical experience, slowing of adduction was usually bilateral, and bilateral slowing was found even in some cases with what appeared to be a unilateral internuclear ophthalmoplegia clinically. As has also been noted by Bird and Leech (1976), unilateral or bilateral slowing of ocular abduction was commonly also present in patients with internuclear ophthalmoplegia. This may be due to involvement of the sixth nerve itself in the pons or of the connections between the pontine reticular formation and the sixth nerve nucleus (Rothstein and Alvord, 1971), or of supranuclear pathways. Involvement of supranuclear pathways is also the most likely explanation for the conjugate gaze paresis and for the global changes in saccade reaction times and velocities found in some patients. The impaired saccade accuracy (saccade dysmetria), which was an isolated finding in some patients, may occur with lesions at different levels in the ocular motor pathway but it is seen most typically with cerebellar lesions (Baloh, Honrubia and Sills, 1979).

Similar parameters of saccadic movements to those measured in the present study were evaluated by Solingen *et al.* (1977) in a small group of patients with well-documented multiple sclerosis and minimal or no clinical abnormalities of eye movement. These workers found abnormalities in 8 of 12 patients studied fully, saccade dysmetria being the most frequent abnormal finding. The present findings in a large group of patients show that any one or more of the three saccade parameters studied may show an abnormality in the individual patient, and that the highest yield is obtained when all three are measured. The advantage of this more detailed form of saccade analysis over the isolated saccade velocity test (Baloh *et al.*, 1975; Mastaglia *et al.*, 1976*a*, 1977) is therefore apparent.

We have not studied the effect of changes in head position on saccade parameters, but Gresty (1977), who measured saccadic velocities in 5 patients with multiple sclerosis, has shown that subclinical abnormalities may be disclosed by performing electro-oculography with the head in eccentric positions.

The degree of recovery in patients who previously had well-documented bilateral internuclear ophthalmoplegia is of interest. Thus, in some, the saccadic studies were entirely normal, while in others, the only remaining clue was the fact that, in contrast to the findings in normal subjects, adducting velocities were slower than abducting velocities although still within the normal range. The normal findings with the full saccade analysis in 2 patients who had previously shown abnormalities with the saccade velocity test also illustrates the capacity for functional recovery in the ocular motor pathway.

The high frequency of abnormalities of pursuit movements found reflects the sensitivity of the pursuit system to organic cerebral disease. Abnormalities may occur with lesions at various sites from the peripheral vestibular system to the frontoparietal cortex (Baloh *et al.*, 1979). In view of the multifocal nature of the demyelinating process in multiple sclerosis the ocular motor pathways could be involved at a number of different levels in the brain-stem, diencephalon, or cerebral hemisphere. The dissociated involvement of saccadic and pursuit movements found in some patients points to differential involvement of the CNS pathways concerned which are separate in their supranuclear course (Gay and Newman, 1972). The increased yield of abnormalities in patients in whom both types of study were performed indicates that they are complementary when subclinical abnormalities of eye movement are being sought in patients with suspected multiple sclerosis.

The contribution of quantitative electro-oculography in the diagnosis of multiple sclerosis was compared to that of pattern-reversal VEP recording which was also carried out in all patients in the present series (Table 7). It was found that the eye movement studies gave a higher yield of subclinical abnormalities than the VEP in patients in the *suspected* and *early probable or latent* categories. The finding of VEP abnormalities in some patients with normal eye movement studies and *vice versa* indicates that the two types of study are complementary and that their combined use will increase the likelihood of detecting subclinical lesions in the CNS in patients suspected of multiple sclerosis. As we have pointed out elsewhere (Mastaglia *et al.*, 1979), such a finding may allow invasive neuroradiological procedures to be avoided in a significant number of such patients.

We conclude that the techniques used provide a sensitive means for analysing the saccadic and pursuit eye movement systems. Because of the fact that they allow subtle or subclinical abnormalities of eye movement to be detected, they are particularly useful in the investigation of patients who present with symptomatic lesions of the spinal cord or visual pathways and who are suspected of having multiple sclerosis. Quantitative electro-oculography is therefore a valuable adjunct to the cerebral evoked potential techniques which may be used to detect subclinical involvement of CNS pathways in multiple sclerosis.

SUMMARY

Ocular movements were studied in 108 patients with established or suspected multiple sclerosis using an on-line computer-based electro-oculographic technique. In one group of patients peak eye movement velocities alone were measured during horizontal refixation saccades. In a second group saccade reaction times and accuracies were measured in addition to velocities, while in a subgroup a quantitative analysis of horizontal pursuit eye movements was also carried out.

With the saccade velocity test abnormalities were present in 44 per cent of cases studied and were subclinical in 18 per cent. Abnormalities were found in 57 per cent of cases in whom the detailed saccade analysis was performed, including 48 per cent of patients with clinically normal eye movements. Saccade reaction time and accuracy were more sensitive parameters than saccade velocity, and the highest yield of abnormalities was obtained when all three were taken into consideration. Abnormalities of pursuit movements were found in 71 per cent of cases studied and were frequently subclinical. Abnormalities of saccadic and pursuit movements were not always present together in the same patient, and the overall yield of abnormalities was higher when the results of both types of study were taken into account.

The yield of abnormalities with the eye movement studies was somewhat lower than with the pattern-reversal VEP in the *clinically definite* multiple sclerosis group, but was higher in patients in the other categories. Subclinical abnormalities of eye movement were found in a significant number of patients with normal VEPs. The finding of such an abnormality in patients with spinal cord syndromes allowed reclassification of 14 patients to a category with a higher degree of diagnostic certainty. It is concluded that quantitative electro-oculography is a valuable adjunct to the clinical evaluation of eye movements and has an important role in the investigation of patients suspected of multiple sclerosis.

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REFERENCES

BALOH, R. W., HONRUBIA, V. and SILLS, A. (1979) Eye tracking and optokinetic nystagmus. *Annals of Otology, Rhinology and Laryngology*. In press.

—— KONRAD, H. R., SILLS, A. W. and HONRUBIA, V. (1975) The saccade velocity test. *Neurology, Minneapolis*, **25**, 1071–1076.

BIRD, A. C. and LEECH, J. (1976) Internuclear ophthalmoplegia. An electro-oculographic study of peak angular saccadic velocities. *British Journal of Ophthalmology*, **60**, 645–651.

BLACK, J. L., MASTAGLIA, F. L. and COLLINS, D. W. K. (1978) On-line electro-oculography. *Journal of Biomedical Computing*, **9**, 393–404.

COLLINS, D. W. K., BLACK, J. L. and MASTAGLIA, F. L. (1978) Pattern-reversal visual evoked potential. Method of analysis and results in multiple sclerosis. *Journal of the Neurological Sciences*, **36**, 83–95.

GAY, A. J. and NEWMAN, N. M. (1972) Eye movements and their disorders. In: *Scientific Foundations of Neurology*. Edited by M. Critchley, J. O'Leary and B. Jennett. London: Heinemann, pp. 126–138.

GRESTY, M. (1977) Eccentric head positions reveal disorders of conjugate eye movement. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 992–1002.

HALLIDAY, A. M., MCDONALD, W. I. and MUSHIN, J. (1973) Visual evoked responses in diagnosis of multiple sclerosis. *British Medical Journal*, **4**, 661–664.

MCDONALD, W. I. and HALLIDAY, A. M. (1977) Diagnosis and classification of multiple sclerosis. *British Medical Bulletin*, **33**, 4–8.

MASTAGLIA, F. L., BLACK, J. L., CALA, L. A. and COLLINS, D. W. K. (1977) Evoked potentials, saccadic velocities, and computerised tomography in diagnosis of multiple sclerosis. *British Medical Journal*, **1**, 1315–1317.

—— —— —— —— (1979) The contribution of visual and somatosensory evoked potentials and quantitative electro-oculography in the diagnosis of multiple sclerosis. In: *Evoked Potentials*. Edited by C. Barber. Lancaster: MTP Press; *Proceedings, International Evoked Potential Symposium, Nottingham, September, 1978*. In press.

—— —— and COLLINS, D. W. K. (1976*a*) Saccadic velocities in multiple sclerosis. *Lancet*, **ii**, 1359.

—— —— —— (1976*b*) Visual and spinal evoked potentials in diagnosis of multiple sclerosis. *British Medical Journal*, **2**, 732.

—— —— —— (1976*c*) Evoked potential studies in neurological disorders. *Proceedings of the Australian Association of Neurologists*, **13**, 15–23.

OCHS, A. L., HOYT, W. F., STARK, L. and PATCHMAN, M. A. (1978) Saccadic initiation time in multiple sclerosis. *Annals of Neurology*, **4**, 578–579.

ROTHSTEIN, T. L. and ALVORD, E. C. (1971) Posterior internuclear ophthalmoplegia. A clinicopathological study. *Archives of Neurology, Chicago*, **24**, 191–202.

SOLINGEN, L. D., BALOH, R. W., MYERS, L. and ELLISON, G. (1977) Subclinical eye movement disorders in patients with multiple sclerosis. *Neurology, Minneapolis*, **27**, 614–619.

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THE CONTRIBUTION OF THE 'SECOND' VISUAL SYSTEM TO DIRECTED VISUAL ATTENTION IN MAN

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INTRODUCTION

IN a recent paper, Mountcastle (1978) discusses the dominant role of the posterior parietal cortex in the control of visual attention. Electrophysiological observations suggest that the parietal lobe contains a mechanism for shifting the focus of visual attention to events of interest, thus 'executes a matching function' between objects of significance in the environment and the internal state of the organism (Hyvärinen and Poränen, 1974; Lynch, Mountcastle, Talbot and Yin, 1977; Robinson, Goldberg and Stanton, 1978).

Some authors have found it useful to distinguish between the 'first' and 'second' visual systems, the former depending mainly on the geniculostriate pathway, and the latter on the colliculus-pulvinar-parietal lobe pathway (Schneider, 1969; Ingle, 1967; Trevarthen, 1968). The first system is said to be concerned with the identification of objects whereas the second is concerned with the detection of events, their location in space, and the control of orientating responses to them for subsequent identification by the first system. Consistent with the inclusion of the parietal lobe in the second system are the clinical findings that patients with lesions of the parietal lobe are, in general, inattentive to the contralateral visual field, for example, they find difficulty in looking towards targets presented there, and are either slow or unable to shift their gaze from object to object within this area (Patterson and Zangwill, 1944; Hécaen and de Ajuriaguerra, 1954; Oxbury, Campbell and Oxbury, 1974). Removal of the posterior parietal cortex in monkeys produces comparable attentional disorders (Bates and Ettlinger, 1960; Ettlinger and Kalsbeck, 1962; Mendoza and Thomas, 1975), and similar symptoms of 'neglect' for the contralateral half of the visual field have also been observed in monkeys after collicular (Denny-Brown, 1962; Wurtz and Goldberg, 1972; Keating, 1974, 1976; Butter, Weinstein, Bender and Gross, 1978) and pulvinar lesions (Ungerleider and Christensen, 1977). The superior colliculus and the n. pulvinar, therefore, may be important components of the central neural mechanism responsible for the detection and localization of events in visual space. In contrast, 'blinded' monkeys (with bilateral striate cortex ablations), can still detect and localize stimuli with a high degree of accuracy as judged by their reaching towards briefly presented visual stimuli randomly located in their visual fields (Weiskrantz, Cowey and Passingham, 1977). Analogous results were obtained in patients with a hemianopia due to damage to the geniculostriate visual pathways; such patients are able to make accurate saccadic eye movements to targets presented at different positions within their blind hemifield (Pöppel, Held and Frost, 1973; Weiskrantz, Warrington, Sanders and Marshall, 1974; Perenin and Jeannerod, 1975; Zihl, 1979). Thus, despite damage to the 'first' (geniculostriate) visual system and a consequent loss of sight, detection and localization of objects in visual space is surprisingly not impaired.

Recently we had the opportunity to test a patient with a suspected lesion incorporating the left pulvinar. The major aim of this study was to determine the attentional defects accompanying this supposed pulvinar lesion. The observed 'neglect' for the contralateral visual hemifield and an impairment of the ability to shift the gaze towards light stimuli presented within it suggest, in agreement with the above observations, that the n. pulvinar could be part of a subcortical system concerned with selective visual attention.

CASE HISTORY

The 63-year old right-handed patient suffered for more than 15 years from a severe diabetes mellitus. She refused treatment of the diabetes mellitus with insulin; the blood sugar level, therefore, had never been regulated satisfactorily. She was known to have had high blood pressure for years but it was untreated. In April 1977, total aphasia developed within several hours. In August and September 1978, psychomotor seizures, dysphasic automatisms and autonomous symptoms were observed, which have increased in number since January 1978.

We examined the patient in July 1978. We found a patient (62 kg/156 cm) with a blood pressure of 150/100 mmHg on both arms. Besides congestion of the liver, moderate signs of venous congestion and cardiacœdema were found. There was marked hyperlipæmia. Hypertensive changes of the retinal vessels were present. The patellar reflexes were abolished, the ankle reflexes diminished. There was marked atrophy of the left quadriceps muscle.

Neuropsychological examination showed a predominant anomic (amnestic) aphasia. In the Sclar Aphasia test, the following deficits were found:

I	Auditory Decoding	18 per cent
II	Visual Decoding	44 per cent
III	Oral Encoding	26 per cent
IV	Graphic Encoding	40 per cent

Conversational speech occasionally was dysprosodic and poorly articulated. The aphasic disorder was accompanied by an aphasic calculation disturbance and alexia with agraphia. A slight constructional apraxia, but no visual spatial disorientation could be demonstrated (fig. 1). (For visual functions *see below*). Simultaneous application of two cutaneous stimuli at symmetrical points of the body revealed no sensory neglect or extinction of sensation. Her performance in a vigilance task (sustained attention) was somewhat below average. Short- and long-term memory performance (ignoring the aphasic disturbance) was only moderately reduced.

A pathological EEG with a δ-focus in the left temporal lobe but without epileptic potentials was repeatedly recorded. The ECG indicated signs of coronary sclerosis. In the EMG the velocity of nerve conduction was reduced in both peroneal nerves, a finding consistent with the clinical assumption of a diabetic neuropathy.

Left internal carotid angiogram (magnification view) showed filling defects in the left common carotid bifurcation, the left carotid siphon and in several branches of the middle cerebral artery. A relevant narrowing of the arterial lumen was seen in the peripheral branches of the left middle cerebral artery only (e.g. in the angular artery). The temporal and temporo-occipital arteries of the middle cerebral artery were not opacified. The patient refused further angiographic investigations; therefore no information about the left posterior cerebral artery and its main branches is available.

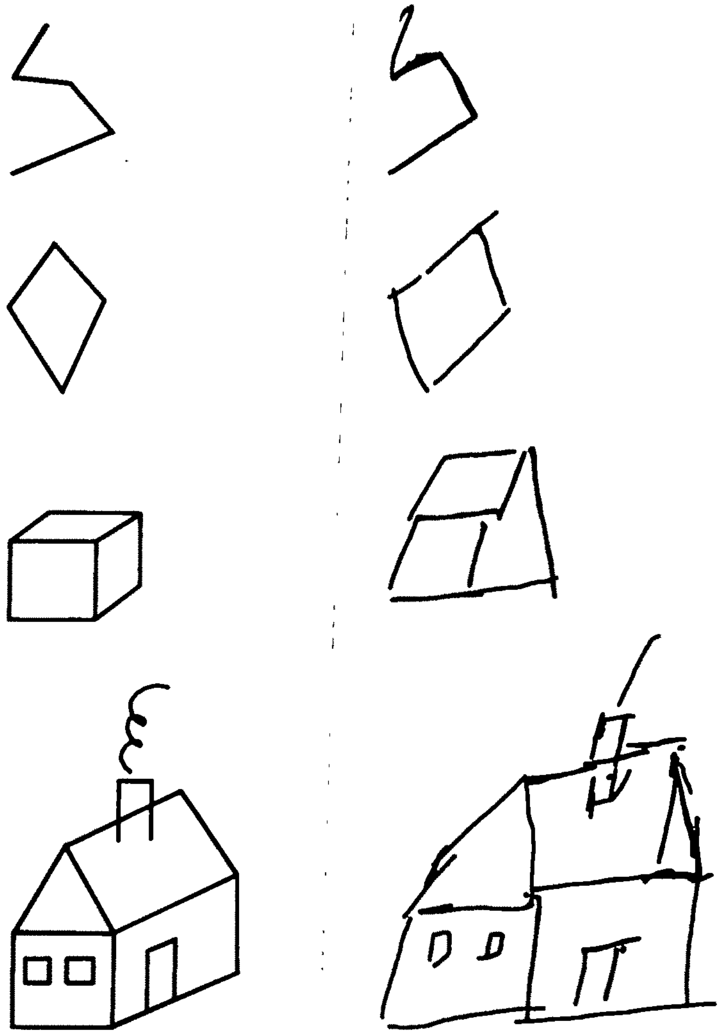


FIG. 1. Model (*left*) and copy (*right*) of a zigzag, a diamond, a cube and a house.

The CT scan (EMI CT 1010) showed an extensive, discontinuous area of low density in the cortex and white matter of the left temporal and parietal lobe (figs. 2A, D). Corresponding segments of the lateral ventricle were markedly enlarged. A small lesion of considerably lower density was found in the left hippocampal formation (fig. 2A). A likewise circumscribed lesion affected the left posterior thalamus, including the n. pulvinar (figs. 2B, C).

In addition, both insular cisterns were moderately widened.

Interpretation of the Main Clinical Findings

The patient suffered from diabetes mellitus with hyperlipæmia and arterial hypertension for a long time without adequate treatment. This increased the speed of development of a generalized atherosclerosis, which could be demonstrated equally in retinal and intracerebral arteries.

The CT scan showed an extensive (ischæmic or embolic?) infarction in the territory of the left middle cerebral artery. The infarcted area affected also the border area between middle and posterior cerebral arteries (*Grenzzoneninfarkt*). The softening in the left hippocampal formation and in the left posterior thalamus indicates the participation of at least some branches of the posterior cerebral artery. The thalamic lesion might be attributed to the territory of the lateral posterior choroid arteries. The branches to the hippocampal formation arise from the ambient segment of the posterior cerebral artery near the origin of the lateral choroidal arteries. The psychomotor seizures might be caused by a hippocampal lesion.

The neuropsychological syndrome seems plausible in the context of the temporo-parietal lesion of the dominant hemisphere if the angular gyrus is included in the infarcted area.

METHODS AND RESULTS

(1) *Visual Field Testing*

The monocular and binocular visual fields were tested by dynamic and static perimetry using the Tübingen perimeter (Sloan, 1971). For *dynamic perimetry*, the target had a diameter of 116 min visual angle; its luminance was 32 cd/m^2. The target was moved with a velocity of about 1 deg s^{-1} from the periphery towards the centre of the visual field. The patient had to push a button whenever she detected the target. *Static perimetry* was performed along the horizontal axis; target diameter was 116′ and 27′ respectively, presentation time was 0.5 s. Target luminance was chosen well above threshold and was then decreased in steps of 0.1 log units. The luminance of the last seen target was defined as threshold when three consecutive targets of 0.1 log units below the threshold were not detected by the patient. *Critical flicker fusion* (CFF) was determined by measuring CFF-fields for 10, 15, 20 and 25 Hz (target: 116′ diameter; 32 cd/m^2). The flickering target was moved with a velocity of about 1 deg s^{-1} from the periphery towards the centre of the visual field. The patient was instructed to push a button whenever she could see the target flickering. The boundaries of the CFF-fields were determined for sixteen meridians; the sequence of measurements along the different meridians was randomized. In addition, CFF was measured randomly for static positions at 40, 30, 25, 20, 15, 10 and 5 degrees eccentricity along the horizontal axis in both visual half-fields. A descending method of limits was used to determine CFF at the different eccentricities. The patient had to push a button when she detected the target flickering.

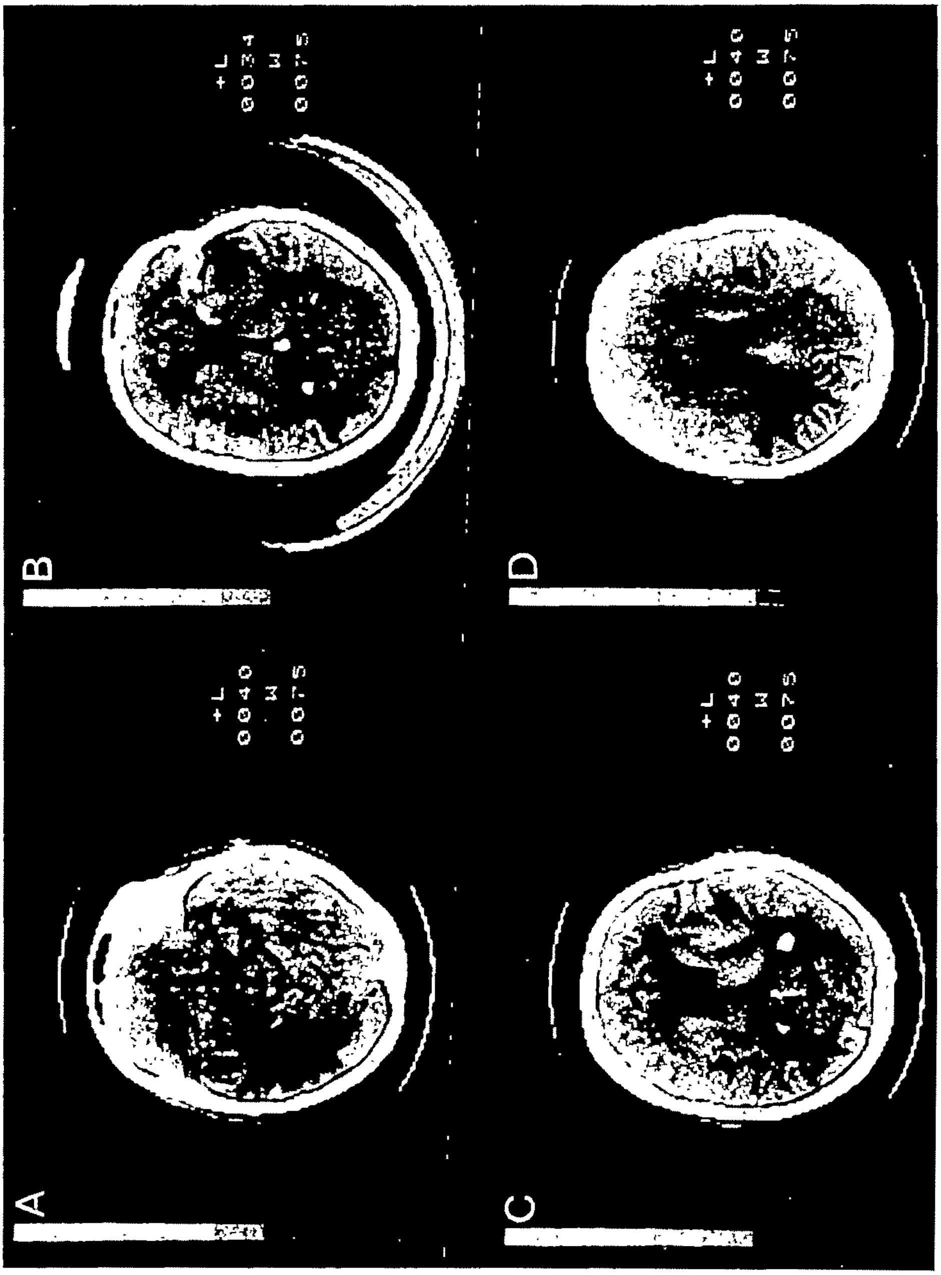


FIG. 2. Results of CT scans obtained at four different levels. For details *see text*.

In all conditions, the patient fixated a red spot of light (diameter 30 ft) in the centre of the homogeneously illuminated hemisphere of the perimeter. Eye position was monitored by a telescope. Background luminance was 3.2 cd/m^2.

Monocular and binocular visual fields were normal; there was no evidence of a retinal or geniculate lesion. Fig. 3 shows the boundaries of the intact binocular visual field. Contrast sensitivity (as defined by the light difference threshold along the horizontal axis) was not reduced in the right visual half-field (that is, contralateral to the pulvinar lesion). In addition, the CFF-fields are shown for the different flickering rates. The CFF-fields for 10 and 25 Hz did not differ significantly in their extent in the left and right visual half-field. In contrast, the CFF-fields for 15 and 20 Hz were clearly contracted in the right as compared to the left hemifield. This inferiority in CFF in the right visual half-field was also found for static positions along the horizontal axis (Table 1). Up to 15 degrees eccentricity, there was no difference between the two visual half-fields; beyond 15 degrees the reduction in CFF increased as a function of eccentricity in the right hemifield (i.e. contralateral to the pulvinar lesion).

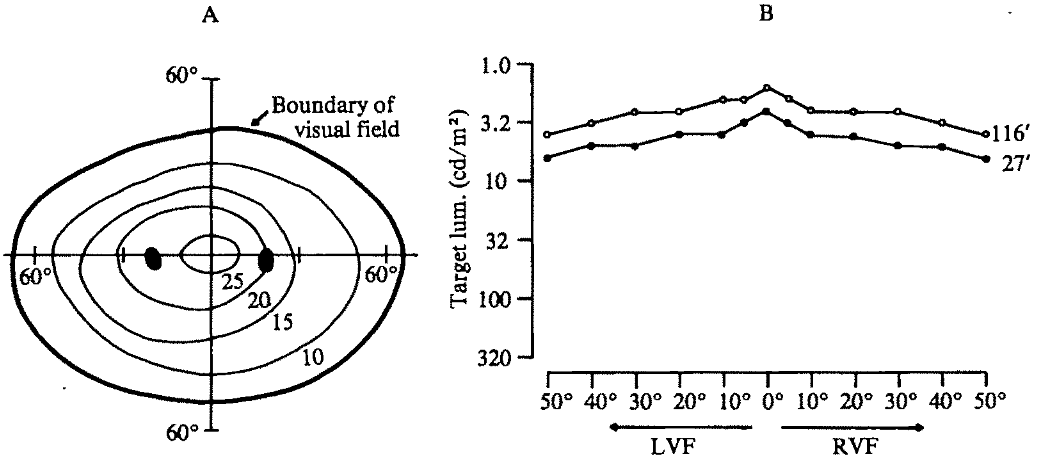


FIG. 3. A, binocular visual field and B, light-difference threshold along the horizontal meridian (LVF = left visual field, RVF = right visual field). In A, boundaries for targets with different flickering rates (10, 15, 20, 25 Hz) are also shown. In B, two different targets (116 min, 27 min) were used to determine contrast-sensitivity.

(2) *Adaptation and Resetting in the Two Hemifields*

Recently it has been shown that the superior colliculus can modulate contrast sensitivity (as judged by increment threshold for light) in a retinotopically organized way. This modulation of contrast threshold was studied using an adaptation technique, that is, by repetitive determination of the increment threshold in a given part in the left or right visual hemifield. In order to test the function of the retinotectal pathway in our patient, the same procedure was employed as in patients with a hemianopia (Singer, Zihl and Pöppel, 1977) and in a patient with a congenital malformation of one superior colliculus (Zihl and von Cramon, 1978; 1979). The Tübingen perimeter was used for this experiment. The patient fixated a red spot of light (30′ diameter). Stationary targets of 116′ diameter were presented for 0.5 s. A psychophysical descending method of limits was used to determine the threshold. Stimulus intensity steps differed by 0.1 log unit. The luminance of the target was changed on every presentation (trial); between 6 and 8 suprathreshold stimuli were presented for each threshold measurement. The intertrial-interval varied between 1 and 2 s; the time between the end of one threshold determination and the beginning of the next threshold measurement was about 5 s. The criterion for the threshold was the same as in static perimetry (*see above*). In the first part of the experiment, the threshold was measured at 30 degrees eccentricity in the temporal visual field of the left eye (that is, ipsilateral to the lesion). The right eye was covered by an opaque occluder. The increase in increment threshold caused by successive measurements was about 0.6 log units. The adaptation showed an almost total transfer between the two eyes indicating its central nature (fig. 4A). In the temporal visual field of the right eye (that is, contralateral to the lesion) no increase in threshold was found after twenty successive measurements (fig. 4B).

TABLE 1. CRITICAL FLICKER FUSION (TWO MEASUREMENTS) IN HZ AS A FUNCTION OF ECCENTRICITY FOR THE LEFT AND RIGHT VISUAL HALF-FIELD

Eccentricity	*Left visual field*	*Right visual field*	*Difference*
5°	26/26	26/26	—
10°	24/24	24/24	—
15°	23/23	22/22	1
20°	23/23	19/19	4
25°	23/23	18/18	5
30°	21/22	16/17	5
40°	18/18	12/12	6

Note the difference in CFF between the left and right hemifield beyond 15 degrees eccentricity.

In the second part of the experiment the interaction between the two visual half-fields (binocular condition) was tested. The threshold was measured repeatedly (as described *above*) at 30 degrees eccentricity in the left visual half-field (ipsilateral to the lesion) and once again a decrease in contrast sensitivity was obtained. Control measurements after 2 min showed no spontaneous recovery. Then the threshold was measured at 30 degrees eccentricity in the right visual half-field (mirror symmetrical position, contralateral to the lesion). Immediately after this stimulation the threshold was measured again in the left visual half-field. As can be seen from fig. 5, adaptation was abolished after the measurements at the mirror position. Thus in the visual half-field contralateral to the lesion there was no adaptation, but resetting could be demonstrated.

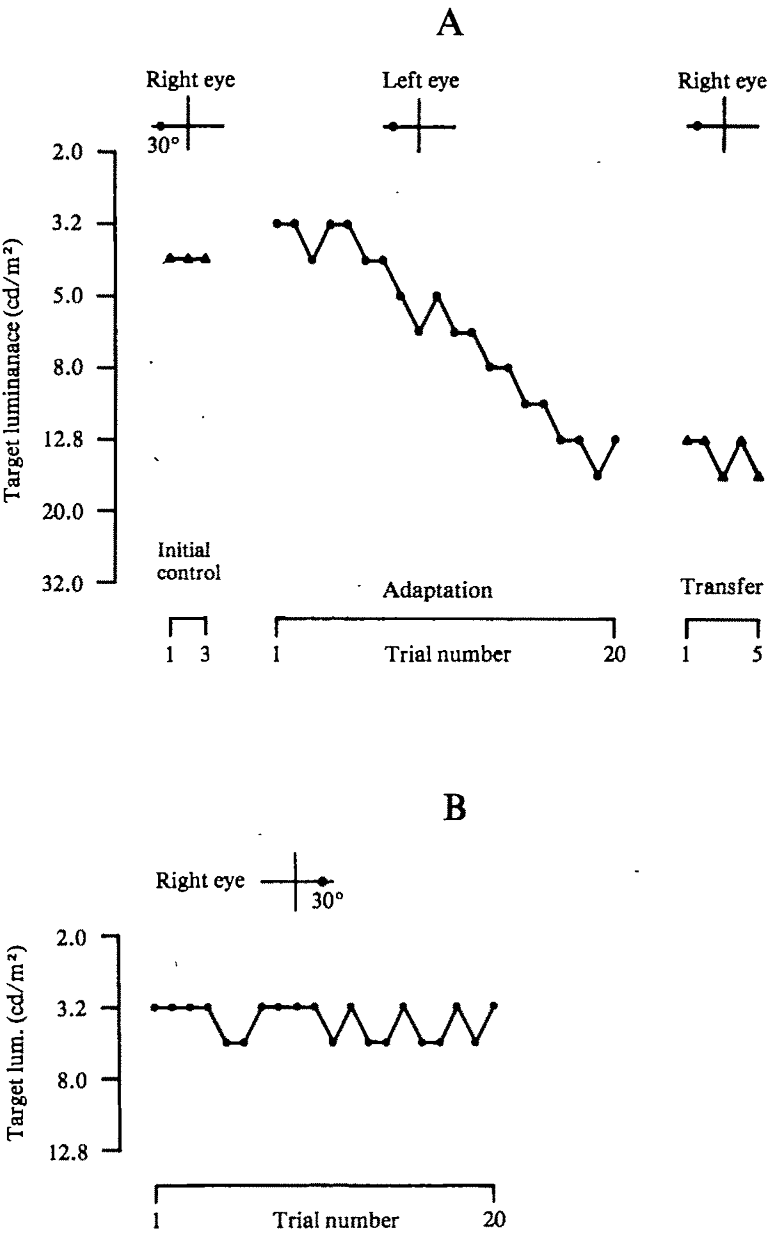


FIG. 4. A, adaptation (left eye, temporal visual field) and interocular transfer (right eye, nasal visual field). B, failure to obtain adaptation in the temporal visual field of the right eye (i.e., contralateral to the lesion). Visual field position is shown in the inserts at the top of the figure. For details *see text*.

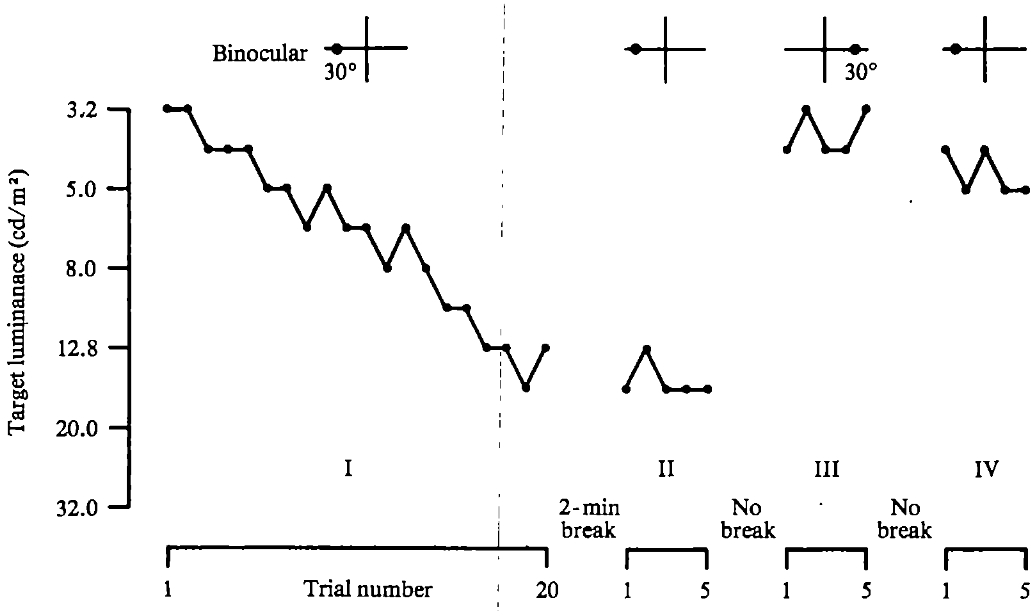


FIG. 5. Adaptation (I) and control measurements (II) in the left hemifield (binocular condition), stimulation at the mirror-symmetric position in the right half-field (III) and immediate resetting of threshold elevation (IV). For details *see text.*

(3) *Simultaneous Bilateral Stimulation*

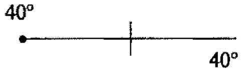
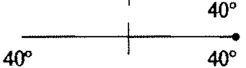
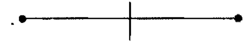
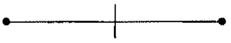
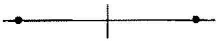
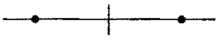
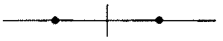
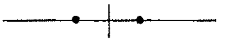
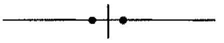
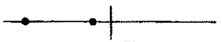
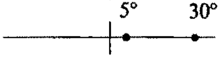
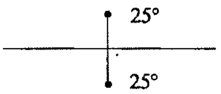
The following experiments were carried out over three two-day periods, when clinical examinations were also conducted. The patient was seated 120 cm in front of a black wall in a windowless darkened room. Fixation was maintained on a red spot of light (diameter: 1 degree, luminance 2.4 cd/m^2), which was projected from behind. Targets were presented simultaneously in the left and right visual half-fields (binocular condition) using two projection tachistoscopes also placed behind the subject. Target luminance was adjusted by neutral density filters. Presentation time, interstimulus interval and time between trials were controlled by electronic circuitry. Eye position was recorded binocularly using a DC-system located behind the subject.

The patient was instructed to fixate the red spot of light and to indicate by finger pointing whether she saw one (on the left or right side) or two light stimuli. She was not allowed to make head movements.

Targets of 0.5 degrees diameter (luminance 1.3 cd/m^2; contrast ratio to background 13:1) were presented for 5 ms at 40 degrees eccentricity in the left or right (unilateral condition) or in the left and right visual half-field (bilateral simultaneous stimulation). Intertrial-interval was 5 s for both conditions. In the unilateral condition (50 trials), all targets presented on the left side, but only 22 (44 per cent) targets presented on the right side were detected by the patient. When two targets were presented simultaneously, one in the left and one in the right visual half-field at 40 degrees eccentricity, the patient pointed only to the target presented in the left in all 100 trials, but never to the target presented in the right visual hemifield, indicating a total 'neglect' for this position in the hemifield contralateral to the pulvinar lesion (Table 2A). Even when she was informed that targets would also appear on the right side, she detected these targets only two or three times. As a control of the patient's detection strategy, blanks were interspersed. Only one (at the left or right side) or no target was presented. No false reactions were observed for this control condition.

In order to investigate this 'neglect' phenomenon in more detail, position in the visual field (eccentricity), size and luminance of the targets and temporal properties

TABLE 2. RESPONSES (%) TO UNILATERAL OR SIMULTANEOUS BILATERAL STIMULATION AT DIFFERENT ECCENTRICITIES

Condition	*Responses (%)*			
A	*Both*	*Left*	*Right*	*No response*
40° 		100		—
40° 			44	56
40° 40° 	—	100	—	—
B				
40° 	—	94	—	6
30° 	—	96	—	4
25° 	2	84	10	4
20° 	66	30	4	—
10° 	88	4	8	—
5° 	90	6	4	—
C	*Both*	*One*		*No response*
30° 5° 	100	—		—
5° 30° 	4	96		—
D	*Both*	*Upper*	*Lower*	*No response*
25° 25° 	80	8	6	6

Positions of stimulation are indicated by black dots. For details *see text.*

(length of presentation and interstimulus interval) were varied. In each condition 50 trials were carried out. Intertrial-interval was always 5 s. Detection performance was measured in terms of percentage correct responses (i.e. when both targets were detected).

(*a*) *Simultaneous bilateral stimulation at different eccentricities.* Target size: 0.5 degrees, target luminance: 1.3 cd/m^2; presentation time: 5 ms. The different locations of bilateral presentation were randomized. The results are shown in Table 2B. The detection performance for both stimuli decreased as a function of eccentricity; beyond 25 degrees the patient detected the target on the left side only in most of the trials.

(*b*) *Simultaneous double stimulation in the same hemifield.* Targets were presented at 5 and 30 degrees eccentricity in the left or right hemifield. Stimulus parameters and presentation time as in (*a*). As can be seen from Table 2C, the patient detected both targets presented simultaneously in the left half-field with high accuracy. When both targets were presented in the right half-field, the patient pointed only to the target appearing near the fovea (at 5 degrees eccentricity) in most of the trials. This result confirms the observations in (*a*) indicating that the 'neglect' is limited mainly to the periphery of the right visual hemifield.

(*c*) *Simultaneous double stimulation in the upper and lower hemifield.* In order to test whether the observed 'neglect' was a phenomenon particularly of the left and right periphery, targets were presented at 25 degrees eccentricity in the upper and lower periphery of the visual field. The results (Table 2D) show quite a good (although not perfect) performance in detecting both stimuli presented along the vertical axis.

(*d*) *Variation of presentation time, temporal separation and target size and luminance.* The effect of exposure duration on detection performance is shown in Table 3A. Target size was 0.5 degrees in diameter, target luminance 1.3 cd/m^2. Targets were presented only in one hemifield or simultaneously at 30 degrees eccentricity in the left and right visual hemifield. Increasing presentation time resulted in an improvement in the detection performance for the periphery of the right hemifield. The data for the left hemifield stimulation (100 per cent correct responses) are not shown in the Table.

When the target in the left hemifield was presented for 5 ms and the target in the right hemifield for 20 ms, the patient's detection performance for both targets was over 80 per cent correct responses. In order to test whether this increase in performance was really a function of exposure time or whether it was due to temporal separation, different interstimulus intervals were used. Target size and luminance were the same as in the last experiment. Results are shown in Table 3B; they demonstrate the increase in the percentage of correct responses as a function of interstimulus interval. When the two targets were separated by 20 ms, no 'neglect' could be obtained for the periphery of the right hemifield.

TABLE 3. RESPONSES (%) TO UNILATERAL OR BILATERAL STIMULATION AS A FUNCTION OF EXPOSURE TIME

Condition	*Responses (%)*			
	Both	*Left*	*Right*	*No response*
A Exposure time				
30° ——+——• 5 ms			44	66
——+——• 50 ms			85	15
30° 30° •——+——• 50 ms 50 ms	85	9	6	—
•——+——• 5 ms 20 ms	82	8	6	4
B Interstimulus interval				
0	—	96	—	4
10 ms	68	16	10	6
20 ms	92	2	2	4
C Target size				
0.5° 0.5° •——+——•	—	98	—	2
1° 1° •——+——•	—	92	6	2
0.5° 1° •——+——•	40	18	36	6
0.5° 3° •——+——•	64	—	36	—
D Luminance (cd/m²)				
1.3 1.3 •——+——•	—	96	—	4
6.8 6.8 •——+——•	4	72	20	4
1.3 16.6 •——+——•	24	12	60	4

For details *see text.*

In the next experimental condition, size and luminance of the targets were varied. In Table 3C the effect of target size on detection performance is shown. Increasing the size of both targets (1 degree in diameter; luminance: 1.8 cd/m²) did not influence detection performance, but increasing the size of the target presented in the right hemifield (1 degree and 3 degrees, respectively; luminance: 1.8 and 2.2 cd/m²) resulted in an improvement in detecting this target. Similar results were obtained when the luminance of the target on the right side was increased (16.6 cd/m²; contrast ratio left:right = 1:13.7). Increasing the luminance for both targets (from 1.3 to 6.8 cd/m²), however, did not result in an increase in the percentage correct responses (Table 3D).

(*e*) *'Extinction' phenomenon during bilateral simultaneous stimulation at 20 degrees eccentricity in the right visual half-field.* During the experiments on bilateral simultaneous stimulation at 20 degrees eccentricity (*see* (*a*) *above*) an unusual phenomenon was observed. After about 30 trials the patient pointed only to the target presented in the left hemifield, even though up to this trial number she had detected both targets. In order to study this phenomenon further, targets (0.5 degrees, 1.3 cd/m^2; 5 ms presentation time) were presented simultaneously at 10, 20 or 30 degrees eccentricity in both visual half-fields. Table 4 shows the responses for Trial No. 20 to the end of the experiment (Trial No. 50) for the three different eccentricities. The extinction phenomenon occurred only at 20 degrees eccentricity for Trial No. 36 onwards, but not for the position nearer to (10 degrees) or more distant from the fovea (30 degrees eccentricity).

TABLE 4. 'EXTINCTION' PHENOMENON DURING SIMULTANEOUS BILATERAL STIMULATION AT 20 DEGREES ECCENTRICITY

Stimulus No.	*Responses*									
	10° 10°			20° 20°			30° 30°			
	Both	*Left*	*Right*	*Both*	*Left*	*Right*	*Both*	*Left*	*Right*	*No response*
20	+			+				+		
21	+			+				+		
22	+			+				+		
23	+			+			+			
24	+			+				+		
25	+					+		+		
26	+			+				+		
27	+			+				+		
28	+			+						+
29	+				+				+	
30		+		+				+		
31	+			+				+		
32	+			+				+		
33	+					+		+		
34	+		+	+						+
35	+			+				+		
36	+				+			+		
37	+				+			+		
38	+				+			+		
39	+				+			+		
40	+			+				+		
41	+				+					+
42	+				+			+		
43	+				+			+		
44		+			+			+		
45	+				+			+		
46	+				+			+		
47	+				+			+		
48	+				+			+		
49	+				+			+		
50	+				+			+		

Note the failure to detect both targets after Trial No. 35. For 30 deg eccentricity the target in the left visual hemifield was detected only.

(*f*) *Bilateral simultaneous stimulation: data from normal subjects.* Two normal inexperienced subjects (67 and 25 years old, respectively) participated in the following experiments. In the first experiment, targets with a diameter of 0.5 degrees (luminance: 1.3 cd/m^2) were presented for 5 ms at 40 degrees eccentricity in the left and right visual half-field. The instructions were the same as those given to the patient. Both subjects showed a high accuracy in detecting both targets (Table 5A). In the second part of the experiment, the size of the target and its luminance were increased in the right visual half-field only (3 degrees diameter and 16.6 cd/m^2, respectively; *see* (*d*). Fifty trials were presented for each condition. Neither the increase in target size nor in luminance reduced the percentage correct responses (Table 5B). The results were similar for both subjects, indicating that age did not influence detection accuracy. Furthermore, it seems unlikely that the phenomenon of 'extinction' results from artefacts in the experimental situation or the instructions.

(*g*) *Oculomotor behaviour: spontaneous lateral eye movements, saccadic responses and saccadic latencies.* In the breaks between the different experimental conditions we observed a paucity of spontaneous lateral saccades towards the right side. To study this phenomenon further, spontaneous lateral saccades were recorded for 6.5 min. The patient kept her eyes at the fixation point for 10 s in order to get a 'steady state' position as a reference line. Then she was instructed that a longer break would be made and that she did not need to maintain fixation during this break. At

TABLE 5. RESPONSES (%) IN 2 NORMAL SUBJECTS TO SIMULTANEOUS BILATERAL STIMULATION (A), AS A FUNCTION OF TARGET SIZE (B) AND LUMINANCE (LEFT TARGET: 1.3 CD/M^2, RIGHT TARGET: 16.6 CD/M^2) ECCENTRICITY WAS 40 DEGREES IN ALL THREE CONDITIONS

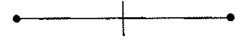
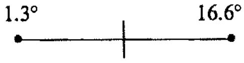
	Responses (%)			
	Both	*Left*	*Right*	*No response*
A 40° 40° 				
Subject 1	96	—	—	4
Subject 2	98	2	—	—
B 0.5° 3° 				
Subject 1	90	—	10	—
Subject 2	92	—	8	—
1.3° 16.6° 				
Subject 1	88	—	12	—
Subject 2	84	—	16	—

TABLE 6. OCULOMOTOR BEHAVIOUR IN THE PATIENT AND IN A NORMAL SUBJECT

	To left	To right
A *Spontaneous saccades*		
Patient (n = 130)	62	38
Normal subject (n = 137)	51	49
B *Saccadic responses*		
Patient (n = 70)		
Correct responses	67	33
Opposite direction	13	9
No response	20	58
Normal subject (n = 35)		
Correct responses	94	96
Opposite direction	—	—
No response	6	4
C *Saccadic latencies (ms)*		
Patient (n = 50)		
Mean	423.5	574.4
95% conf. limits	400.6–446.5	518.1–631.3
Range	266–600	330–1066
Normal subject (n = 30)		
Mean	286.5	267.6
95% conf. limits	275.8–297.3	256.2–279.0
Range	200–400	200–400

For details *see text.*

the end of the break the patient was asked to direct her eyes once more to the fixation point and this position was recorded again for 10 s. As can be seen in Table 6A, there is a clear minority of spontaneous saccades to the right side (contralateral to the lesion). Since this recording was performed in the same darkened room and the apparatus was placed behind the subject (both the EOG recording system and the experimenter were located behind a wooden partition), it seems very unlikely that there were any lateralization cues in the darkened room. For comparison (and also for control), spontaneous lateral eye movements were recorded in a normal subject (67-years old) under the same conditions. In this case, no lateralization of spontaneous saccades was observed (Table 6A).

It has been shown in a prior experiment (Table 2A), that the patient often did not respond when the target was presented only in the right side of the hemifield. We repeated this experiment using visually elicited saccadic eye movements. The target was presented without an auditory warning for 5 ms, either in the left or right visual half-field at 30 degrees eccentricity. Target size was 0.5 degrees, target luminance 1.3 cd/m^2. The patient was asked to make a saccade towards the target presented in the left (or right) side. In the first part, targets appeared only in the left visual hemifield and in the second part only in the right hemifield. A paper velocity of 30 mm/s (1 mm corresponding to 33 ms) was used to evaluate the latency of the saccades.

As just observed in the previous experiment with unilateral stimulation, the patient failed to respond consistently when the target was presented in the right hemifield. Sometimes, also, when targets were presented in the left hemifield no saccadic response could be elicited even though the patient indicated that she had detected the target. For a normal subject (Subject 1), over 90 per cent correct responses to unilateral stimulation was observed (Table 6B). The difficulty in shifting the gaze towards targets presented in the right hemifield was also evident from the delay in the initiation of visually evoked saccadic eye movements. The time between the offset of stimulus and the start of the saccadic response to the right side was markedly increased; the difference as compared to the left side was about 150 ms. In addition, the latencies for saccadic responses to the left hemifield were also increased; the difference from the normal subject was about 140 ms. One may argue that all reaction times are generally increased in the patient and therefore also the latency for visually evoked saccades. The measurement of the visual and acoustic simple reaction time showed, however, that there may be a dissociation of simple hand reaction time to light stimuli and latency for visually evoked saccades. For measurement of hand reaction time, 30 consecutive stimuli were presented, and the patient was instructed to react as quickly as possible to the appearance of each stimulus. The first 10 measurements were taken as a training period. The temporal interval between succeeding stimuli was random, ranging from 2 to 7 s and averaging 4 s. After 10 measurements a break of half a minute was introduced. Mean reaction time to visual stimuli was 279.45 ms (SD ± 51.26), to acoustical stimuli it was 205.15 ms (SD ± 41.65). As reaction time of the saccadic movement is approximately in the same range as that of a hand response to a visual stimulus (Diefendorf and Dodge, 1908; Zihl, 1979), the increased saccadic latency in our patient may result primarily from the damaged left pulvinar. The different presentation times in the two conditions (5 ms exposure duration in the 'saccadic movement' condition and 150 ms in the 'hand response' condition) cannot account for the observed dissociation in the reaction time to visual stimuli. Exposure duration affects hand reaction time below about 50 ms presentation time; the difference, however, is only of the order of 10 ms (Wells, 1913). In addition, control measurements using targets with longer exposure durations (500 ms) showed similar saccadic latencies for the patient.

DISCUSSION

'Neglect' for the Contralateral Hemifield

It has been suggested that the 'second' visual system plays an important role in the control of directed visual attention (Mountcastle, 1978). In addition, neurophysiological observations of monkeys (Goldberg and Wurtz, 1972; Schiller and Malpeli, 1977) and psychophysical data from humans concerning collicular function (Singer *et al.*, 1977; Zihl and von Cramon, 1979) have been interpreted in terms of the selective control of attention within the visual field. No attempt has been made, however, to test visual attention at a behavioural level.

In our patient the most striking abnormality was a 'neglect' for the periphery of the visual hemifield contralateral to the pulvinar lesion. This was judged by a decrease in the percentage of correct responses of pointing to the target presented in the right half-field (appearing simultaneously with one in the left). However, the degree of this 'neglect' was related both to the position in the right hemifield and to stimulus parameters such as size and luminance.The 'neglect' was only apparent at positions greater than 20 degrees eccentricity in the right hemifield and thus supports the idea that the 'second' visual system is important in the analysis of objects appearing in the periphery of the visual field. Although the 'neglect' was always apparent at greater than 20 degrees eccentricity, at 20 degrees eccentricity it only developed after about 30 trials. No explanation is, as yet, available for this 'extinction' phenomenon in this part of the right visual half-field.

Further, increasing the relative size or luminance of the target presented in the periphery of the right hemifield, or increasing either the length of target presentation or the temporal separation between the target appearing in the left then right hemifield reduced the degree of the 'neglect'.

To our knowledge, this is the first report of a visual 'neglect' observed in a patient suffering from a lesion including the n. pulvinar. This 'neglect' for visual stimuli presented briefly in the right visual half-field was not accompanied by a contralateral 'visuospatial' neglect for visual objects, as observed in patients with parietal lobe lesions (Warrington, 1969; Oxbury *et al.*, 1974). Such 'visuospatial' neglect is qualitatively distinguishable in being an inability to recognize part of an object or to reproduce this part when requested (cf. our patient, fig. 2). Thus, our patient exhibited a single distinctive type of neglect: a reduced ability to detect light stimuli in the periphery of the right visual half-field, that is, that contralateral to the pulvinar lesion, especially during presentation of two simultaneous stimuli.

Oculomotor Responses

Although eye movements were essentially normal, oculomotor behaviour was, in fact, noticeably altered. The poverty of spontaneous horizontal eye movements and the increased latencies of visually evoked saccades directed towards the right visual hemifield are consistent with observations in monkeys subjected to pulvinar (Ungerleider and Christensen, 1977) or collicular lesions (Wurtz and Goldberg, 1972; Latto, 1978). As reported by Heywood and Ratcliff (1975), a patient with unilateral colliculectomy exhibited a similar significant asymmetry of spontaneous saccades; no differences were found, however, in the latency of saccades to targets presented in the hemifield contralateral to the lesion. In our patient latency was, in fact, also increased for visually elicited fast eye movements to the left hemifield. One could argue, therefore, that the increased saccadic reaction time to the right hemifield is composed of, first, a difficulty in the shift of fixation from an original point (which also affected saccadic reactions to the left) and, secondly, of an increased latency for saccadic eye movements to targets in this hemifield contralateral to the lesion reflecting an attentional deficit with respect to this side. This effect was the only abnormality manifested in both visual hemifields, and one can speculate as to a role of both pulvinars in the change of position of fixation irrespective of the original and subsequent direction of gaze (Ungerleider and Christensen, 1977). Although anatomical investigations have not yet demonstrated a direct interpulvinar pathway, an interaction mediated via an indirect pulvinar—cortex-pulvinar connection—which certainly exists (Benevento and Davis, 1977; Chalupa, 1977)—is quite possible.

Collicular Function—Adaptation and Resetting

As anticipated, an increase in the increment threshold (that is, a decrease in the ability to distinguish a target from a background of differing luminance) occurred, as in normal subjects, after repeated measurement of this contrast threshold in the periphery of the left visual half-field. This decreased sensitivity of the peripheral visual field is in contrast with the foveal situation where such a decrease is not observed (Singer *et al.*, 1977). In the periphery of the right visual hemifield (contralateral to the pulvinar lesion), no increase in the light-difference threshold was obtained. This observation suggests that the modulation of light-difference threshold is mediated by the superior colliculus (Zihl, von Cramon, Pöppel and Singer, 1979) and its projection to the visual cortex via the n. pulvinar. The interruption of this pathway at the level of the pulvinar would explain the lack of adaptation in the right visual hemifield.

After such adaptation at a position in the peripheral visual field, the original sensitivity can be restored by stimulation of the mirror position in the opposite visual half-field. In our patient such a resetting was apparent, suggesting that this is purely a consequence of an interaction between the colliculi, as has been previously discussed by Sprague (1966) for the cat and by Pöppel and Richards (1974) for the human visual system. Further, initial contrast sensitivity (prior to any adaptation) was not diminished in either visual half-field of our patient, whereas this was impaired both in a patient with a collicular lesion (Zihl and von Cramon, 1979) and in monkeys after collicular ablation (Latto, 1977).

Collectively, the above observations provide evidence that collicular function was probably unaffected by the lesion incorporating the n. pulvinar. The abnormalities in visual function observed in our patient, therefore, may be interpreted as primarily consequences of the pulvinar lesion.

Eccentricity-specific Dissociation of Critical Flicker Fusion

In the normal unrestricted visual field of our patient (suffering from a lesion incorporating the left pulvinar), a marked reduction was found in the critical flicker fusion (CFF) only for the periphery of the right visual hemifield. A similar reduction in CFF in the right visual half-field was observed in a patient with a left collicular lesion (Zihl and von Cramon, 1978), whereas in patients with lesions of the geniculostriate visual pathway a reduction in CFF was found only for the parafoveal region (Pöppel, von Cramon and Backmund, 1975). The 'second' visual system may, therefore, play a critical role in the processing of rapidly presented visual stimuli in the periphery of the visual field, but, as the peripheral CFF was only partially depressed, the involvement of an additional system (probably the 'first' visual system) in this function should also be taken into consideration. The particular contribution of the 'second' visual system to the differentiation of rapidly presented stimuli appearing in the periphery of the visual field may be an attentional one. Since the size of the visual field capable of distinguishing repeated stimuli at less than 15 Hz was the same for both hemifields, the attentional component of processing rapidly presented stimuli is presumably of greater importance at higher frequencies (cf. fig. 3 and Table 1).

In conclusion, one prominent function of the tectopulvinar extrastriate visual system may be in the control of the direction and, perhaps, the 'intensity' of visual attention. The detection of objects in the peripheral part of the visual field is often a prerequisite for their subsequent foveation, and, in this respect, the pulvinar appears to be critical for fovea-mediated pattern discrimination (Chow, 1954; Chalupa, Coyle and Lindsley, 1976; Chalupa, 1977). An unilateral depression of pulvinar function may result in a 'neglect' of the contralateral hemifield due to an inability to shift visual attention to this side. As an indirect consequence, saccadic responses to objects appearing in the contralateral hemifield are diminished or their latencies are abnormally prolonged.

SUMMARY

The visual functions of a patient suffering from a brain lesion incorporating the left n. pulvinar was examined in order to assess the contribution of this structure to human vision. With the exception of the following abnormalities visual functions were normal. First, there was a decrease in the critical flicker frequency in the periphery (but not in the parafoveal region) of the right visual hemifield, that is, that contralateral to the pulvinar lesion. However, the second and most striking characteristic was—as shown by presenting visual stimuli bilaterally and simultaneously—a 'neglect' for the periphery of this contralateral visual half-field. This 'neglect' was a function of (*a*) position in the visual field (eccentricity), (*b*) stimulus properties (size and luminance), (*c*) temporal properties (length of presentation and interstimulus interval). In addition to this reduced capacity to detect stimuli appearing in the periphery of the right visual hemifield, there was also prolonged latency of visually evoked saccadic eye movements and a paucity of spontaneous eye movements directed towards the right visual hemifield. These results are interpreted in terms of a contribution of the n. pulvinar to the detection of light stimuli presented in the periphery of the visual field, and support the view that the tectopulvinar extrastriate visual pathway plays an important role in the control of visual attention.

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REFERENCES

BATES, J. A. V. and ETTLINGER, G. (1960) Posterior biparietal ablations in monkeys. Changes to neurological and behavioral testing. *Archives of Neurology, Chicago*, **3**, 177-192.

BENEVENTO, L. A. and DAVIS, B. (1977) Topographical projections of the prestriate cortex to the pulvinar nuclei in the macaque monkey: an autoradiographic study. *Experimental Brain Research*, **30**, 405-424.

BUTTER, C. M., WEINSTEIN, C., BENDER, D. and GROSS, C. G. (1978) Localization and detection of visual stimuli following superior colliculus lesions in rhesus monkeys. *Brain Research, Amsterdam*, **156**, 33-49.

CHALUPA, L. M. (1977) A review of cat and monkey studies implicating the pulvinar in visual function. *Behavioral Biology*, **20**, 149-167.

—— COYLE, R. S. and LINDSLEY, D. B. (1976) Effect of pulvinar lesions on visual pattern discrimination in monkeys. *Journal of Neurophysiology*, **39**, 354-369.

CHOW, K. L. (1954) Lack of behavioral effects following destruction of some thalamic association nuclei in monkey. AMA *Archives of Neurology and Psychiatry*, **71**, 762-771.

DENNY-BROWN, D. (1962) The midbrain and motor integration. *Proceedings of the Royal Society of Medicine*, **55**, 527-538.

DIEFENDORF, A. R. and DODGE, R. (1908) An experimental study of the ocular reactions of the insane from photographic records. *Brain*, **31**, 451-489.

ETTLINGER, G. and KALSBECK, J. E. (1962) Changes in tactile discrimination and in visual reaching after successive and simultaneous bilateral posterior parietal ablations in the monkey. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 256-268.

GOLDBERG, M. E. and WURTZ, R. H. (1972) Activity of superior colliculus in behaving monkey. II. Effect of attention on neuronal responses. *Journal of Neurophysiology*, **35**, 560-574.

HÉCAEN, H. and DE AJURIAGUERRA, J. (1954) Balint's syndrome (psychic paralysis of visual fixation) and its minor forms. *Brain*, **77**, 373-400.

HEYWOOD, S. and RATCLIFF, G. (1975) Long-term oculomotor consequences of unilateral colliculectomy in man. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications*. Edited by G. Lennerstrand and P. Bach-y-Rita. Oxford: Pergamon Press, pp. 561-564.

HYVÄRINEN, J. and PORÄNEN, A. (1974) Function of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain*, **97**, 673-692.

INGLE, D. (1967) Two visual mechanisms underlying the behaviour of fish. *Psychologische Forschung*, **31**, 44-51.

KEATING, E. G. (1974) Impaired orientation after primate tectal lesions. *Brain Research, Amsterdam*, **67**, 538–541.

—— (1976) Effects of tectal lesions on peripheral field vision in the monkey. *Brain Research, Amsterdam*, **104**, 316–320.

LATTO, R. (1977) The effects of bilateral frontal eye-field, posterior parietal or superior collicular lesions on brightness thresholds in the rhesus monkey. *Neuropsychologia*, **15**, 507–516.

—— (1978) The effects of bilateral frontal eye-field, posterior parietal or superior collicular lesions on visual search in the rhesus monkey. *Brain Research, Amsterdam*, **146**, 35–50.

LYNCH, J. C., MOUNTCASTLE, V. B., TALBOT, W. H. and YIN, T. C. T. (1977) Parietal lobe mechanisms for directed selective attention. *Journal of Neurophysiology*, **40**, 362–489.

MENDOZA, J. E. and THOMAS, R. K. (1975) Effects of posterior parietal and frontal neocortical lesions in the squirrel monkey. *Journal of Comparative and Physiological Psychology*, **89**, 170–182.

MOUNTCASTLE, V. B. (1978) Brain mechanisms for directed attention. *Journal of the Royal Society of Medicine*, **71**, 14–28.

OXBURY, J. M., CAMPBELL, D. C. and OXBURY, S. M. (1974) Unilateral spatial neglect and impairments of spatial analysis and visual perception. *Brain*, **97**, 551–564.

PATTERSON, A. and ZANGWILL, O. L. (1944) Disorders of visual space perception associated with lesions of the right cerebral hemisphere. *Brain*, **67**, 331–358.

PERENIN, M. T. and JEANNEROD, M. (1975) Residual vision in cortically blind hemifields. *Neuropsychologia*, **13**, 1–7.

PÖPPEL, E., HELD, R. and FROST, D. (1973) Residual visual function after brain wounds involving the central visual pathways in man. *Nature, London*, **243**, 295–296.

—— and RICHARDS, W. (1974) Light sensitivity in cortical scotoma contralateral to small islands of blindness. *Experimental Brain Research*, **21**, 125–130.

—— VON CRAMON, D. and BACKMUND, H. (1975) Eccentricity-specific dissociation of visual functions in patients with lesions of the central visual pathways. *Nature, London*, **256**, 489–490.

ROBINSON, D. L., GOLDBERG, M. E. and STANTON, G. B. (1978) Parietal association cortex in the primate: sensory mechanisms and behavioral modulations. *Journal of Neurophysiology*, **41**, 910–932.

SCHILLER, P. H. and MALPELI, J. G. (1977) Properties and tectal projections of monkey retinal ganglion cells. *Journal of Neurophysiology*, **40**, 428–445.

SCHNEIDER, G. E. (1969) Two visual systems. *Science*, **163**, 895–902.

SINGER, W., ZIHL, J. and PÖPPEL, E. (1977) Subcortical control of visual thresholds in humans: Evidence for modality specific and retinotopically organized mechanisms of selective attention. *Experimental Brain Research*, **29**, 173–190.

SLOAN, L. L. (1971) The Tübingen perimeter of Aulhorn and Harms. *Archives of Ophthalmology*, **86**, 612–622.

SPRAGUE, J. M. (1966) Interaction of cortex and superior colliculus in mediation of visually guided behavior. *Science*, **153**, 1544–1547.

TREVARTHEN, C. B. (1968) Two mechanisms of vision in primates. *Psychologische Forschung*, **31**, 299-337.

UNGERLEIDER, L. G. and CHRISTENSEN, C. A. (1977) Pulvinar lesions in monkeys produce abnormal eye movements during visual discrimination training. *Brain Research, Amsterdam*, **136**, 189-196.

WARRINGTON, E. K. (1969) Constructional apraxia. In: *Handbook of Clinical Neurology*. Volume 4. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland Publishing Company, pp. 67-83.

WEISKRANTZ, L., COWEY, A. and PASSINGHAM, C. (1977) Spatial responses to brief stimuli by monkeys with striate cortex ablations. *Brain*, **100**, 655-670

—— WARRINGTON, E. K., SANDERS, M. D. and MARSHALL, J. (1974) Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain*, **97**, 719-728.

WELLS, G. R. (1913) The influence of stimulus duration on reaction time. *Psychological Monographs*, **15** (5, Whole No. 66).

WURTZ, R. H. and GOLDBERG, M. E. (1972) Activity of superior colliculus in behaving monkey. IV. Effects of lesions on eye movements. *Journal of Neurophysiology*, **35**, 587-596.

ZIHL, J. (1979) 'Blindsight': Improvement of visually guided eye movements by systematic practice in patients with cerebral blindness. *Neuropsychologia*. In press.

—— and VON CRAMON, D. (1978) Perimetric testing of superior colliculus function in man: A case study. *Nervenarzt*, **49**, 488-491.

—— —— (1979) Midbrain function in human vision. *Experimental Brain Research*, **35**, 419-424.

—— —— PÖPPEL, E. and SINGER, W. (1979) Interhemispheric modulation of light-difference threshold in the periphery of the visual field. In: *Structure and Function of the Cerebral Commissures*. Edited by I. S. Russell, M. W. van Hof and G. Berlucchi. London: Macmillan Press, pp. 421-427.

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NOTICES OF RECENT PUBLICATIONS

Selected Writings of Sir Charles Sherrington. Compiled and Edited by D. Denny-Brown. Reprinted 1979. Pp. 532. Oxford University Press. Price £15·00.

This book, originally published in 1939 under the sponsorship of the Guarantors of Brain, contains a carefully arranged selection of papers and parts of papers designed to reveal the development and scope of Sir Charles Sherrington's researches. Those of his observations regarded as of particular interest to neurologists are given precedence, but many of his more theoretical contributions are also included. In the edited papers care has been taken to preserve sufficient context to avoid misrepresentation yet at the same time minimize reduplication. This approach has permitted a clear outline of all Sherrington's researches with the exception of those already comprehensively dealt with in his classical monograph *The Integrative Action of the Nervous System.*

Sherrington's prolific investigations were instrumental in laying the foundations for a scientific approach to neurology. His experiments threw new light on many bewildering clinical findings and consequently his work represented an inspirational source to neurologists fifty years ago. Neurophysiology has expanded rapidly in recent years and many of the questions posed by his integrative approach to synaptic mechanisms have now been answered by his illustrious pupils. Insights of great clinical relevance have also occurred in the related disciplines of neurochemistry, neuroimmunology and neuropharmacology. This wealth of new knowledge has tended to distance a new generation of neurologists from the importance of his pioneering work, and to many it probably remains only in the form of semi-automatic thought processes, or general principles. The reprinting of this book, therefore, offers a welcome opportunity to re-examine in some detail the scientific method and results of Sherrington's endeavours.

The papers have been grouped into chapters which deal successively with the organization of motor and sensory nerve roots, the spinal and postural reflexes, reciprocal innervation and the motor area of the cerebral cortex. Finally some of Sherrington's most important contributions on the nature of excitation and inhibition are included, followed by a complete bibliography of his work. Dr Denny-Brown has also provided helpful summaries at the beginning of each chapter and numerous footnotes indicate the original source of the publications. Sherrington, in order to explain certain features of reflex activity, was obliged to collect elementary information on how muscles were innervated from the spinal cord and how sensory nerves entered. The first two chapters deal with these anatomical investigations which he performed on Macacus rhesus and the cat. Using a technique in which he sectioned three roots above and below the root under study and then selectively stimulated its central and peripheral branches, he was able to map out the nerve supply of muscles and skin. Sherrington demonstrated that each motor root supplies a fused parallel ray of muscles extending distally and that stimulation produces a complex movement without physiological significance. This led to his concept of the myotome as a series of parts of many muscles and explained why trauma to the cord never completely paralysed any one muscle, and why section of a ventral root causes weakness of a number of muscles. He also drew attention to the close analogy between the dermatomes of man and monkey and showed that sensory root supply derives its form from anatomical segmentation, diverging widely from the nerve supply to muscles. He stressed the remarkable overlapping of sensory roots to the skin compared with peripheral nerve trunks and showed in tame animals that the fields for heat and pain were less extensive than those for light touch. These chapters are particularly valuable in illustrating the meticulous thoroughness of his scientific method.

Further evidence of Sherrington's initial desire to explain neuronal function in histological terms comes from his work on the course of reflex connections in the spinal cord and his attempts to localize motor function in the cortex. Only a selection of his observations on the physiological anatomy of the spinal cord are included here but greater attention is given to his studies with Grunbaum and Graham Brown on the motor cortex. Using 22 chimpanzees, 3 mountain gorillas and 3 orang-utans Sherrington demonstrated the inherent functional instability of the cerebral cortex and also its capacity to refine voluntary movement by breaking up compound movements already formed by lower centres. He also showed that pareses caused by cortical ablation were usually temporary and did not entirely depend for recovery on adjoining areas or matching cortical points in the contralateral hemisphere.

The remaining chapters are principally concerned with Sherrington's two outstanding achievements: the discovery of the innate pattern of reciprocal innervation and his concepts of synaptic inhibition. Reciprocal innervation had already been hinted at by Charles Bell but it was Sherrington's systematic analysis which clarified the mechanism by which an antagonist relaxes as a protagonist contracts. His studies implied that the afferent nerves must establish a central excitatory state in one group of neurons while initiating a central inhibitory state in a different portion of the motor neurone pool. This has frequently been misrepresented to signify that whenever flexor muscles contract, extensors relax and vice versa. Sherrington's studies on double reciprocal innervation, reproduced fully here, clearly show that he was well aware that this was not always the case.

Full descriptions of the spinal animal and the decerebrate preparations are given. Studies on the spinal dog and cat convinced him that spinal shock did not arise from physical trauma but was largely due to the removal of excitatory cerebral influences. He also used the spinal animal to observe the recovery of reflexes and documented the early return of the nociceptive flexion reflex and crossed extensor response in the dog with the later return of the extensor thrust reflex. He noted impaired temperature regulation below the cord transection and excitability of reflexes immediately above (Schiff-Sherrington phenomenon) and as well as describing many new reflex effects, made cogent observations on the phenomenon of paraplegia-in-flexion.

His rediscovery of the decerebrate preparation, however, provided the model from which his most important findings come. By supplying a background of sustained excitation he was able to begin to discover how neurons could be actively silenced. His conception of postural reflexes also stemmed from this work giving impetus to research into all the problems related to sustained muscular contraction. He was able to demonstrate that stimulation of either the dorsal column or the cerebellum could inhibit reflexes in the decerebrate preparation, observations now being put to practical use in the treatment of spasticity, and it is also clear from his writings that he was well aware that decerebrate rigidity required intact afferent supply.

It was from the study of three reflexes that most of Sherrington's ideas developed in relation to inhibition and reciprocal innervation. From work on the ipsilateral flexor reflex with its extensive receptive field he arrived at the inevitable conclusion that convergence of afferents towards a final common path, the motor neuron, must occur. He stressed that a reflex response is graded, does not obey the all-or-none law, and depends on the strength of the initial stimulus. Important concepts such as subliminal fringe with temporal and spatial summation, after discharge and reflex fatigue, were also largely based on experiments with the ipsilateral flexor reflex and the polysynaptic scratch reflex. The crossed extensor reflex added the useful idea of recruitment which implies that under prolonged afferent stimulation reflex tension may rise gradually and not in the more explosive *d'emblée* fashion of nociceptive flexion.

It is to be regretted that room could not be found in this book for Sherrington's paper published in 1894 on the anatomical constituents of nerve and muscle, in which one finds his masterly description of the muscle spindle. This basic observation enabled him later to show conclusively that muscle sense existed and that spindles were capable of responding to stretch and contraction.

It is within the general framework of this work on postural sense that the stretch reflex with its short latency and absence of after-discharge proved most valuable. Studies with this reflex permitted him to show that extensor muscles in the decerebrate preparation could maintain tone despite great variations in length. The lengthening reaction or clasp-knife effect was clearly demonstrated suggesting to Sherrington that inhibitory mechanisms exist to enable the muscle to yield to a potentially injurious force.

Many of Sherrington's intuitive principles have now been verified using new experimental methods. For example, his concepts of central inhibitory and excitatory states were largely based around the idea of algebraical summation of two antagonistic processes occurring at different kinds of synapse but striking a balance point at the motor neuron. His evidence in favour of an active inhibitory process all centred around arguments dependent on the demonstration of identical properties for inhibition and excitation disregarding sign. In recent years, Sir John Eccles using microelectrode intracellular recording techniques in the grey matter of the spinal cord has shown that localized depolarization of a nerve cell produces an excitatory post-synaptic potential (EPSP) whereas localized hyperpolarization increases the membrane potential and opposes neuronal discharge causing an inhibitory post-synaptic potential (IPSP). It has also become possible to explain these opposing mechanisms in terms of release of inhibitory and excitatory neurotransmitters from separate synaptic junctions.

Nevertheless modification of Sherrington's original concept of a single nerve fibre with both excitatory and inhibitory branches has been necessary with evidence now being in favour of separate inhibitory circuits containing at least one interneuron. Microelectrode studies have also demanded the accommodation of historically divergent mechanisms such as that of pre-synaptic inhibition in which one afferent terminal blocks excitation through another.

Our awareness of the complexity of servo-mechanisms in the control of voluntary movement and the importance of the gamma loop has increased greatly in recent years. Furthermore the recording of reflexly evoked potentials from ventral roots has provided quantitative information concerning central reflex effects and made it possible to distinguish between monosynaptic and polysynaptic reflexes. Sherrington's archetypal 'simple reflex', the flexor reflex, is now known to be polysynaptic and his concept of occlusion has not been reproducible with newer experimental methods. Despite this the overall picture of reflex taxis remains virtually as Sherrington left it and it is only the spinal machinery not the end result of its action which has been found to be different.

Sir Charles Sherrington's monumental work has now become the foundation upon which much of modern neurophysiology has been built. His best papers, many of which are contained in this volume, combine artistic spontaneity with impeccable scientific method, and the pattern of organization of spinal reflexes he elucidated is still essential to our understanding of nervous function. The reprinting of this book will provide valuable source material for the neurophysiologist, and for the neurologist an opportunity to re-examine in functional terms the abnormal physical signs encountered in clinical practice. It may also be recommended to all neuroscientists from which it is to be hoped the lessons of logical thought, meticulous observation and scientific imagination, which so characterize Sherrington's work, may be learned.

A. J. LEES

Programs of the Brain. By J. Z. Young. 1978. Pp. 325. Oxford University Press. Price £5·95.

The will of Lord Gifford (who desired that lecturers under his bequest should promote 'Natural Theology') has had not a few distinguished interpreters from the ranks of brain science. In this book, based on the 1975–7 Gifford Lectures at Aberdeen, J. Z. Young joins the succession with a characteristically lively and instructive series of essays. His general theme is that 'a good method (of describing the operations of whole masses of nervous tissue) may be to say that brains contain programs that regulate our lives' (p. 1.). For some reason he seems to regard his claim as novel and contentious. 'Not many physiologists will be ready to accept the wide interpretations I am giving about the programs of the brain', he says on p. 256, after quoting Tylor's piquant remark that 'conservatism and unreflectiveness are two major features of savagery'. Physiologists who would rather be deemed reflective than savage may, however, be reassured. By the end of the book the metaphor of 'programs' is in greater danger of seeming platitudinous than outrageous. Perhaps that is a measure of the author's persuasive artistry.

Young agrees with Luria that 'even the most sophisticated computers provide a hopelessly inadequate means of speaking about say, the creativity of humans' (p. 41). He argues, however, that the *principles* of information transfer, and in particular the computer scientist's concept of a hierarchy of controls, provide essential mental tools for the understanding of brain functions. This claim is surely indisputable, especially when carefully qualified by reminders (e.g. on pp. 62 and 95) that the processing, addressing and storing of information are probably done on different principles in brains and computers. 'The brain even at birth is not a general-purpose computer into whose memory *any* information can be placed... (The) very existence (of memory) is only possible as part of that program of events that we call a lifetime' (pp. 78, 79). In passing, it seems a pity that the author favours the computer engineer's usage whereby a 'memory' can mean a piece of hardware (more properly called a 'store') as well as the information stored in it, and/or the conscious human experience of remembering. The suggestion that this usage 'has led to clarification of the language with which we talk about that function in ourselves' (p. 79) is not too well supported.

Young is most at ease in explicating the anatomical and physiological discoveries that bear on his topic. Drawing on his experience of cephalopod systems, he proposes that learning and memory (even longer-term) depend on the production by amacrine cells of inhibitory transmitters, to suppress unwanted connections and so leave others to become established. The theme of 'pain' is pursued in some detail, with entertaining asides on such matters as the neural projection of the whiskers of the mouse (for which the reference to Woolsey and van der Loos on p. 110 should read (1970)). Vision gets an extensive discussion, which incorporates Zeki's recent anatomical findings as well as some much-needed current changes in emphasis as to the form of representation of the visual world required in the brain. Young accepts that 'we can regard all seeing as a continual search for the answers to questions posed by the brain' (p. 119). (It might have been useful to point out the difference that this makes to the old conundrum of perceptual stability during exploratory eye movements). He is critical of the notion that we have specific 'grandmother's-face cells' for recognizing individual objects, preferring the hypothesis that perceptual integration is 'a property of *groups* of neurons' (p. 128). In this connection there is a slip of the pen on p. 212, where Young speaks of the left cortex of a 'split-brain' patient as 'alone receiving visual signals from the right eye'. Here 'eye' should read 'visual half-field'.

Other topics on which the author provides a wealth of information include 'Hearing, speaking and writing', 'Knowing and thinking', and 'Sleeping, dreaming and consciousness'. Most controversial, perhaps, are his sprightly explorations of such matters as 'Needing, nourishing and valuing' and 'Believing and worshipping'. It is right, of course, to insist on the impossibility of sharply separating the brain processes active in value-judgement from those of precise logical reasoning. 'The cerebral activities of every man are a unity' (p. 134). But does it follow from this (or anything else) that it is 'deceptive and dangerous' of Popper to claim that questions of the truth of a belief must be sharply distinguished from questions of its psychological or historical origins? The computer analogy itself would tend to support Popper; for however closely integrated might be the workings of a computer (including its programs), there is still an essential difference between asking (*a*) *how* it came to a given conclusion, and (*b*) whether that conclusion is *true*. Even without the help of brain science, we know that conclusions which turn out to be true can sometimes be reached by invalid reasoning or irrational hunch—and vice versa.

What then of religious belief, and the stated concern of Lord Gifford's bequest? Like William James, J. Z. Young rejects any implication that religious experience should be dismissed as 'nothing but' expressions of our organic disposition. He has perceptive things to say about the social as well as the personal functions of belief in God. In detail, however, both the accuracy and the tendency of his analysis are open to question. Does his claim (p. 258) that 'rejection of the world of intellect' is 'characteristic of Christianity' apply to the Christian founders of the Royal Society, for example? How far in practice could he defend the dogma (p. 259) that 'what each of us feels as a worthwhile aim for life is *for that very reason* worthwhile' (my italics)? (How would that formula work in the case of Hitler, say, or Stalin, or Idi Amin?) And does it really follow (p. 267) that if we had complete certainty about what we ought to do, 'we should . . . then be subject to a strong form of determinism'? The theory that people are bound to do what they know to be right may be charitable in intention; but many of us would have to join St. Paul (Rom. 7:18) in lamenting our failure to confirm it in practice!

But assessments of this *tour de force* as a contribution to natural theology will doubtless be made elsewhere. Here, let J. Z. have the last word (p. 259): 'Our religion or our irreligion are social. Yet we are each alone with the universe'.

D. M. MACKAY

NEW BOOKS ON CLINICAL NEUROIMMUNOLOGY

Clinical Aspects of Neuroimmunology. By E. A. NEUWELT and W. K. CLARK. 1978. Pp. 277. Baltimore: Williams and Wilkins. Price $38.50.

Clinical Neuroimmunology. By P. O. BEHAN and S. CURRIE. 1978. Pp. 213. London: W. B. Saunders. Price £12·00.

Clinical Neuroimmunology. Edited by F. C. ROSE. 1979. Pp. 526. Oxford: Blackwell Scientific Publications. Price £25·00.

Neurochemical and Immunologic Components in Schizophrenia. By D. BERGSMA and A. L. GOLDSTEIN. 1978. Pp. 450. New York: Alan R. Liss. Price $46.00.

It is evident that immunology is assuming an increasingly important role in medicine. In neurology there are well established inflammatory diseases (for example, polymyositis) and those such as multiple sclerosis where defective immunological mechanisms are suspected as key factors in the pathogenesis. The discovery of antibodies to cholinergic receptor protein in myasthenia gravis and the successful treatment of patients by plasma exchange indicates the practical importance of immunology to specific diseases. In addition, development of the technique of radioimmunoassay coupled with the availability of various neural and viral antigens provides the potential basis for dramatic advance in management of patients and understanding of the underlying pathogenesis.

There is therefore a need for publication of a clear account of the principles of immunology and an indication of the clinical application of this information for neurologists. On the other hand basic scientists and research workers require more specialized treatment of the subject together with illustration of the clinical relevance of neuroimmunology. Four recently published books are designed to cater for these various readerships.

The book by two neurosurgeons, Neuwelt and Clark, is intended as an introductory text or reference book dealing solely with neuroimmunology. Since the authors aim at a readership with diverse background the book begins with a brief account of basic immunology. Those unfamiliar with the terminology and concepts of immunology will find the text difficult. The next chapter on neuroimmunological methods is especially valuable but despite ample illustrations and tabulated data, this too is hard going. There follows an account of 'unique aspects of CNS immunology' where the question of immunological privilege of the brain and the origin and properties of microglia are debated. A section on CSF includes two sample case reports of patients, together with the CT scan, radiological and histological findings. The remainder of the book deals with grouped disease entities with clinical and pathological data, in addition to relevant neuroimmunology. There are many tables and diagrams. An account of CNS-tumour immunology (46 pages) and a chapter on the role of immune complexes in neurological disease (39 pages) stand out as being of especial value. Immunology of myasthenia gravis, infections and demyelinating diseases are also covered separately. The book is well produced; there are selected up-to-date references but the index is limited.

The small book by Behan and Currie is designed to provide neurologists with a practical guide to the subject. It is neither intended as a textbook of neurology nor one of immunology. Since these are the objectives the authors could perhaps have omitted much clinical description and pathology which would be familiar to neurologists. In the first chapter there are clear résumés of basic immunology including the processes of cell-mediated and humoral immune responses. This section (19 pages) could usefully have been expanded to include more, for example, on the inflammatory reaction and T-cell subsets. Something on the nature of brain antigens and especially receptor proteins together with a section on radioimmunoassay could be valuable—particularly since RIA can be used to detect viral antigens. In addition more line diagrams would be useful. Each following chapter includes a section on clinical features, laboratory and pathological findings. treatment and ætiology. There is a clear difference in emphasis compared to the previous book. For example, they have devoted a whole chapter to acute hæmorrhagic leucoencephalitis (14 pages) and 11 pages on acute disseminated encephalomyelitis, whereas in Neuwelt and Clark's book these topics only occupy a page. There is relatively little on tumour immunology. Nevertheless Behan and Currie have the rare ability to make the difficult subject readable and understandable, particularly when dealing with the clinical implications of their subject, but I think they should have concentrated on this interface between immunology and neurology more and not attempted to document their chapters so extensively (i.e. about 45 pages of 5,000 references out of 204 pages).

The book edited by Rose is particularly suitable for research workers and specialists. Although at the beginning there are brief accounts of basic immunology, most contributions are from a wide range of experts, basic scientists and clinicians, who attended a symposium in London in 1978. Thus the introductory section is followed by 31 contributions on specialist topics relating to muscle disease, peripheral neuropathies, motor neuron disease, multiple sclerosis, virology, malignancy and therapy. Most of the articles are of a high standard and contain valuable data not otherwise easily available. The emphasis is on the clinical application of immunology and it should therefore be particularly useful to neurologists who are already familiar with the scientific basis of immunology.

The fourth and unusual book, *Neurochemical and Immunologic Components in Schizophrenia*, is also based on an interdisciplinary meeting. The convenors organized a gathering of specialists from diverse areas indirectly or remotely connected with psychiatric illness. On the whole the contributions on the immunology of schizophrenia are unimpressive but there are useful chapters such as that of Jerslid on the HLA system and multiple sclerosis or that on immune complex deposits in the choroid plexus, but this is not the kind of book one would normally read to find this information.

As might have been expected, each of the four books have good and bad points. I think basic scientists and neurosurgeons may prefer Neuwalt and Clark, while neurologists and specialist research workers could be recommended Behan and Currie, and selected articles in Clifford Rose's publication.

A. N. DAVISON

Advances in Biochemical Psychopharmacology. Vol. 19. **Dopamine.** Edited by P. J. ROBERTS, G. N. WOODRUFF and L. L. IVERSEN. 1978. Pp. 422. New York: Raven Press. Price $35.75.

This book is based on a symposium held at the University of Southampton in 1977; this was one of the satellites to the Meeting in Copenhagen of the International Society for Neurochemistry. Although dopamine in all its aspects has been a recurrent subject in recent publications, much new material was presented by nearly 100 contributors. The first chapter brings interesting new developments in the anatomy of the dopaminergic systems, including their neocortical subdivision. Many papers deal with interaction between neurons employing different transmitters among which GABA and substance P figure prominently. Release is increasingly studied in synaptosomal preparations rather than in intact tissue or tissue slices, but *in vivo* methods or isolated tissues remain the method of choice for work on the recently discovered release from dendrites and for the large number of investigations on control by presynaptic receptors of transmitter release and synthesis. Experiments on drug actions suggest the existence of more than one dopamine receptor within single cerebral regions, and explanations of the slow and prolonged therapeutic effect of drugs are now more frequently sought in their effect on gradual alterations of receptor sensitivity than in the impact of the first interaction between drug and receptor. An increasing number of studies is carried out on the nucleus accumbens which, though resembling the caudate nucleus in many ways, also shows differences in responses which might be of clinical and therapeutic importance. It has recently been shown to be affected in Parkinsonism by a loss in dopamine similar to that found in the striatum. On the other hand, the theory that there is increased dopaminergic activity in schizophrenia finds less support than a few years ago. An important finding about the well-known increase by neuroleptics of dopamine turnover is the great difference shown by various dopamine-containing tissues in the development of tolerance to this increase; it is highest in the striatum and lowest or absent in frontal cortex and retina. The book ends with the description of improved methods for the identification by fluorescence microscopy of neurons containing either noradrenaline, dopamine or 5-hydroxytryptamine.

It must be obvious from the examples given that the symposium will be of interest to a large group of readers concerned either with the clinical or the theoretical aspects of dopaminergic neurons.

M. VOGT

Annual Review of Neuroscience. Edited by W. M. COWAN, Z. W. HALL and E. R. KANDEL. 1979. Pp. 555. Palo Alto: Annual Reviews, Inc. Price $17.50.

Beginning in 1932 with *Annual Reviews of Biochemistry*, this outstanding American series has expanded to include, amongst other subjects, physiology, medicine and now neuroscience. Most of the topics chosen for review are of general neurobiological interest. Thus there are four articles relating to vision and a related group on neurotransmission, ion channels, axonal transport, opiate receptors and opioid peptides. The increasing interest in the role of the brain as a target for steroid hormone action is reviewed in another chapter (57 pages).

Of more immediate medical concern is the short rather general article on the biology of affective disorders and the equally brief account of the development of behaviour in human infants. There is also a chapter (31 pages) on slow viral infections in which the pathogenesis of these various diseases is competently and succinctly discussed. The articles are written by acknowledged experts and contribute critical reviews of significant developments.

I think very few will want to read this book from cover to cover, but it can be recommended to libraries as a useful and moderately priced reference book of high scientific standard.

A. N. DAVISON

Dementia. Edited by C. E. WELLS. Second Edition. 1977. Pp. 284. Philadelphia: F. A. Davis. Price £18·15.

The first edition of this book has been immensely popular amongst students of neurology and medical investigators. Interest in dementia is clearly increasing, mainly by the recognition of senile dementia of Alzheimer's type as a growing health problem affecting the Western World. Evidence to this is the publication in 1978 of two volumes containing research papers presented at conferences devoted to senile dementia and closely related disorders.

Nineteen authors have contributed to the book, which is organized into twelve chapters. Haase describes about sixty diseases that cause dementia, while Tomlinson focuses on senile dementia, describing the neuropathology in a lucid manner. Katzman and Roos and Johnson write chapters on normal pressure hydrocephalus and viruses in dementia, respectively. In the chapter on biochemical aspects, McNamara and Appel conclude that relatively little progress has been made since the First Edition towards elucidating the biochemical basis of dementia. They argue that much basic information is needed before we will understand the pertinent biochemical mechanism. This has not, however, daunted others in searching for biochemical evidence of selective neurotransmitter changes in

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